Supreme Court, U.S.
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No.

In the Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

In virtually every patent infringement case, federal district judges are called on to determine the scope of one or more claims in a patent. Such "claim construction" requires the judge to assess not only the state of the art and customary meaning of claim terms at the time of the invention, but also the contemporaneous meaning to a skilled practitioner of both the patent's technical description of the invention and the patent applicant's statements to the Patent and Trademark Office during the prosecution process. Many patent cases also include disputes over the "doctrine of equivalents," a significant doctrine that prevents a copyist from avoiding liability "by making only insubstantial changes to a patented invention." *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 727 (2002); *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997).

This case raises two questions concerning the administration of these important doctrines and the allocation of judicial authority between trial and appellate courts:

1. Are all aspects of a district court's claim construction subject to *de novo* review, as the Federal Circuit has held despite vociferous criticism from numerous judges and commentators, or instead should the Federal Circuit have reviewed the factual determinations underlying the district court's claim construction deferentially?

2. By restricting the ways in which a presumption of "prosecution history estoppel" may be rebutted, and engaging in *de novo* review of a district court's determinations that the presumption *has* been rebutted, has the Federal Circuit effectively resurrected the categorical bar to a claim of infringement under the doctrine of equivalents that was expressly rejected in *Festo* and *Warner-Jenkinson*?

RULE 29.6 STATEMENT

Petitioner Amgen Inc. is a publicly traded corporation, and no publicly held corporation owns more than 10% of its stock.

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PETITION FOR A WRIT OF CERTIORARI

OPINIONS BELOW

The majority and dissenting opinions of the court of appeals (App. 1a-51a) are reported at 457 F.3d 1293. The opinions of the district court (App. 52a-335a) are reported at 339 F. Supp. 2d 202 and 287 F. Supp. 2d 126. Prior opinions of the court of appeals (App. 336a-415a) and the district court App. 416a-593a) are reported, respectively, at 314 F.3d 1313 and 126 F. Supp. 2d 69. The court of appeals' order denying rehearing and six dissenting and concurring opinions (App. 594a-609a) are reported at 469 F.3d 1039.

JURISDICTION

The judgment of the court of appeals was entered on August 3, 2006. The order denying rehearing (App. 595a) was entered on November 22, 2006. On January 29, 2007, Chief Justice Roberts extended the time to petition for a writ of certiorari to and including March 22, 2007. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

RULE INVOLVED

Federal Rule of Civil Procedure 52(a) states:

> In all actions tried upon the facts without a jury or with an advisory jury, the court shall find the facts specially and state separately its conclusions of law thereon * * *. Findings of fact, whether based on oral or documentary evidence, shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge of the credibility of the witnesses. * * *

STATEMENT

This is a case about the proper allocation of power between trial and appellate courts. Two issues that arise in most patent cases – claim construction and prosecution history estoppel – are decided by the court without a jury, but rest on factual findings. This case gives the Court an excellent opportunity to

resolve judicial disagreements about the standard by which the Federal Circuit should review those determinations, and to assess whether the Federal Circuit's reversal of careful and scientifically well-informed district court determinations on both issues comported with this Court's precedents.

In nearly every patent infringement case, a district court must construe the patent's claims – that is, determine their scope. Claim construction requires assessment of essentially factual matters, including: (1) the state of the art at the time of the invention; (2) the customary meaning of the claim terms at the relevant time; (3) the meaning of the patent specification (*i.e.*, the detailed technical description of the invention) to a skilled practitioner; and (4) the significance, again to a skilled practitioner, of the patent applicant's statements to the Patent and Trademark Office ("PTO") during the prosecution process.

In this case, the district judge drew on knowledge he had gained of scientific principles and terminology and carefully construed the term "therapeutically effective amount" in a patent claim in accordance with the understanding of skilled practitioners and the meaning they would give to the specification and prosecution record. A divided panel of the court of appeals, however, thought that the specification said something different. Ignoring all of the district court's detailed determinations, the majority announced a claim meaning broader than what the patent applicant stated was his invention and contrary to the understanding of skilled practitioners in the field. The result was a remand for a *third* trial on the validity of the claim.

What made this imperial act possible was the practice of reviewing claim constructions *de novo*, a practice that has been lambasted for years by bench, bar, and academy because – as this case glaringly demonstrates – it not only produces inaccurate results, but also misallocates judicial resources, spawns needless disputes, prolongs litigation, and destroys certainty. In *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), this Court held that, although claim construction entails evidentiary inquiry, the exercise is better assigned to a trial judge than

a jury. The Federal Circuit has since read *Markman* to mean that claim construction is a purely legal exercise, and announced that it owes no deference to *any aspect* of a district court's claim construction. *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc).

But the Federal Circuit is wrong. Claim construction rests on factual determinations, appellate deference to which is *required* by Federal Rule of Civil Procedure 52(a) and this Court's precedents. The court of appeals' practice, therefore, is strong reason for this Court – which in *Markman* decided the proper role of judge and jury in claim construction – to take the logical next step and decide the proper roles of the trial and appellate courts. This case is a perfect opportunity.

The court of appeals also used *de novo* review to scrap a careful ruling regarding the doctrine of equivalents, which prevents a copyist from avoiding liability "by making only insubstantial changes to a patented invention." *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 727 (2002); *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). *Festo* clarified that the right to claim infringement based on an "equivalent" invention is usually presumptively foreclosed by "prosecution history estoppel" if the patentee amended the patent during prosecution. But not all amendments surrender equivalents, and *Festo* set forth criteria for rebutting the presumption. The district court found those criteria satisfied because the rationale for the amendment in question had nothing to do with the equivalent at issue, and the patentee could not reasonably be expected to have literally claimed the equivalent. In reversing, the Federal Circuit effectively held that an amendment during prosecution surrenders anything beyond the claim's literal terms, thus resurrecting a categorical bar rejected in *Festo* and *Warner-Jenkinson*.

A. Factual Background

The patents at issue cover an anemia drug known as recombinant erythropoietin and manufactured by Amgen under the brand-name Epogen. Described by the district court as

"pathbreaking," App. 494a, the work of the inventor, Dr. Fu-Kuen Lin, provided the first product that could treat various forms of anemia, a condition in which the patient lacks "a steady, sufficient supply of red blood cells." In the body, natural erythropoietin ("EPO") stimulates the production of red blood cells; patients who fail to produce EPO become anemic. "The therapeutic goal for treating [such] patients * * * is to increase and maintain the production of red blood cells." App. 55a, 459a-460a.

Before Dr. Lin's breakthrough inventions, that goal had never been achieved. Small amounts of a form of EPO had been isolated from human urine by Dr. Eugene Goldwasser. When Goldwasser injected this "urinary EPO" into three anemic patients, there was only some suggestion of certain preliminary biological effects – including a reported increase in reticulocytes, the precursors to mature red blood cells – but no increase in any patient's "hematocrit," the ratio of red blood cell volume to total blood volume, which is the standard measure for anemia. In other words, the urinary EPO failed to treat anemia. Dr. Goldwasser eventually abandoned his study and testified that it was a failure. App. 55a, 260a-273a, 459a, 484a-487a. By contrast, the results of Dr. Lin's EPO were "dramatic beyond anyone's dreams." App. 493a (quoting respondents' witness). His EPO – much more potent than and structurally distinct from urinary EPO, and producible in commercial quantities – was "therapeutically effective because it was able to increase and maintain the patients' hematocrit level." App. 339a-340a, 460a, 486a n.27.

B. Earlier Proceedings

1. Amgen brought this action in 1997 seeking a declaration that respondents' EPO product infringed several of Dr. Lin's patents. One of them is U.S. Patent No. 5,955,422 (the '422 patent), Claim 1 of which reads (emphasis added):

> A pharmaceutical composition comprising a *therapeutically effective amount* of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant, or carrier, wherein

said erythropoietin is purified from mammalian cells grown in culture.

Chief Judge Young of the District of Massachusetts presided over the case. He selected a Massachusetts Institute of Technology professor as a technical advisor and "met privately with him for background tutorial assistance." App. 418a. He then conducted a three-day "*Markman* hearing" in which he received demonstrative exhibits and heard argument on ten key claim terms, App. 424a, and later held a 23-day bench trial that included testimony from 30 scientists. App. 419a, 454a-591a.

a. Judge Young found that respondents (collectively "TKT") infringed Claim 1 of the '422 patent. App. 453a. TKT contended that the claim was invalid under 35 U.S.C. § 102 because it was "anticipated" by – *i.e.*, not novel in light of – Goldwasser's urinary EPO. Judge Young rejected that argument because the Goldwasser subjects showed no increase in hematocrit, and "the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit." Judge Young concluded: "Due to this lack of effect upon hematocrit levels, the patients did not appear to receive any health benefits from the reported biologic effects. * * * Consequently, the Goldwasser study could not anticipate any of Amgen's claims requiring a *therapeutically effective amount* of EPO." App. 484a-487a (emphasis added).

b. Judge Young also ruled that TKT infringed U.S. Patent No. 5,621,080 (the '080 patent) under the doctrine of equivalents. Judge Young found that TKT's product met every element of the relevant claims, except for a requirement that the protein have the "erythropoietin amino acid sequence of FIG. 6." Figure 6 of the specification depicts a DNA sequence coding for a polypeptide[1] having 166 amino acids. After the patent was filed, however, scientists learned that the last amino acid is usually cleaved off before the EPO molecule is released from the cell. Amgen's and TKT's EPO products thus have

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[1] A polypeptide is a molecule consisting of a chain of amino acids.

only 165 amino acids. Judge Young determined that the absence of the 166th amino acid was an insubstantial difference with no impact on the molecule's properties. App. 461a-464a, 524a-529a. At the same time, Judge Young rejected TKT's defense of prosecution history estoppel. Even though Amgen amended the patent during prosecution to add the Figure 6 reference to claims that had specified no sequence, the amendment was made solely to avoid potential redundancy with another of Amgen's patents – not the type of reason giving rise to estoppel under *Warner-Jenkinson*. App. 529a-533a.

In closing, Judge Young thanked the parties for teaching him about "the nuances of * * * this rather complicated realm of science." App. 591a.

2. a. In its first decision, the Federal Circuit agreed that TKT infringed the '422 patent, App. 391a, but vacated Judge Young's ruling that Goldwasser's urinary EPO did not anticipate Claim 1. The panel acknowledged, as TKT's experts conceded, that "[t]he therapeutic goal for treating anemic patients is to increase the 'hematocrit level,'" App. 339a – something Goldwasser did not do. But the panel said that the patent specification "appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy." App. 400a.

The panel based that remark on a sentence that said: "to the extent that [the] products of the invention share the in vivo activity of natural EPO isolates" – *i.e.*, insofar as the claimed products produce biological effects similar to those associated with urinary EPO – they are "*suitable for use in [EPO] therapy procedures * * * to develop any or all of the effects here[to]fore attributed in vivo to EPO*, e.g. stimulation of reticulocyte response * * *, erythrocyte mass changes, * * * and, as indicated in Example 10, increasing hematocrit levels." '422 patent, col. 33 (emphasis added). The panel remanded for the district court to construe "therapeutically effective" in light of this sentence, and reevaluate whether Goldwasser's EPO anticipated Claim 1. App. 401a.

b. With respect to the '080 patent, the Federal Circuit held that, under this Court's intervening *Festo* decision, Amgen's amendment presumptively surrendered its claim to TKT's equivalent. The court remanded for a determination whether the *Festo* presumption is rebutted. App. 385a.

C. The District Court's Claim Construction Ruling

1. Judge Young concluded that the term "therapeutically effective amount" requires, *in addition to* certain in vivo[2] effects recited in the specification, "a result that in and of itself helps to heal or cure."[3] In arriving at this construction, Judge Young held another *Markman* hearing in which counsel used demonstrative exhibits and referred to expert testimony. The judge appointed a special master to assist with preparation of the next opinion – 53 pages of which are devoted to explaining his claim construction, see App. 70a-112a – and held a second, nine-day trial on other remanded issues. App. 67a-68a.

Judge Young followed the Federal Circuit's script for claim construction. He began with the term's plain and customary meaning, which he determined from technical and other dictionaries was an amount "that produces healing or curing as it relates to medical treatment of disease." App. 75a-82a. He then determined that the language of the patent claims, the specification, and the prosecution history each supported this meaning. App. 82a-109a. He repeatedly emphasized that his conclusions were informed by the expert testimony and his

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[2] "In vivo" (Latin for "in something living") simply means in a live organism, as opposed to "in vitro" (Latin for "in glass"), meaning in some kind of environment outside a living organism, such as a petri dish.

[3] Here is the court's construction in pertinent part (App. 112a):

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33 * * *: stimulation of reticulocyte response, * * * erythrocyte mass changes * * * and * * * increasing hematocrit levels.

familiarity with the technology, even though expert testimony was not used "to define the term." *E.g.*, App. 85a, 86a n.28, 89a & n.29, 90a-91a & n.30, 109a n.46, 110a-111a n.47.

Judge Young did not think that the sentence to which the court of appeals had pointed equated each of the in vivo effects listed there with a "therapeutically effective" result. To conclude otherwise, he said, would be to endorse a "factually incorrect" proposition. Aside from the basic point that the sentence does not even use the term "therapeutically effective," urinary EPO was already known to elicit some of the listed effects but not an increase in hematocrit, which is how skilled practitioners measure EPO's therapeutic effectiveness. App. 90a-92a. Judge Young noted that "[e]xperts on both sides agree that the biological effects are surrogate markers or early indicators that a therapeutic effect will follow." App. 91a n.30. Therefore, he explained, "this part of the specification does not indicate that these biological responses are sufficient or that Amgen 'broadened' * * * 'therapeutically effective' to encompass the elicitation of biological effects alone regardless of whether they heal or cure." App. 91a-92a.

2. Finally, the district court found that Goldwasser did not anticipate Claim 1. From an exhaustive analysis of the technical testimony, App. 261a-273a, Judge Young concluded that any biological effects obtained by Goldwasser were not therapeutically effective but were "precursory responses before a therapeutic result is achieved." App. 273a.

D. The District Court's *Festo* Ruling

In a separate opinion (App. 278a-335a), Judge Young found that Amgen had rebutted the presumption of prosecution history estoppel that would otherwise have barred its claim of equivalent infringement of the '080 patent. In *Festo*, this Court described three situations in which the presumption is rebutted because "an amendment cannot reasonably be viewed as surrendering" the defendant's equivalent: (1) "the equivalent was unforeseeable"; (2) "the rationale underlying the amendment bears no more than a tangential relation to the equivalent in

question"; or (3) "some other reason * * * suggests that the patentee could not reasonably be expected to have described the insubstantial substitute." App. 294a.

After ruling against Amgen on the foreseeability criterion, Judge Young turned to the second criterion, noting that with this one, "more than the others," what counts is "the *purpose* of the amendment," not simply "whether the amendment itself narrows the * * * claim in a way that affects the equivalent in question." App. 317a-318a. Following a detailed examination of the prosecution history, he ruled for Amgen, finding that it had added the Figure 6 language not to exclude a 165-amino-acid EPO, but to distinguish the '080 patent from another patent known as the '933 patent on the basis that the '080 patent (unlike the '933) covered only *human* EPO. App. 319a-324a.

Judge Young also ruled for Amgen on the third *Festo* criterion. He agreed with TKT that Amgen *could have* drafted the claim differently, but explained that the final criterion calls for a "reasonableness inquiry" into what the patentee "*could be expected* to have done." App. 329a. Not only did the PTO know that the final form of EPO has 165 amino acids, but also, according to unrebutted expert testimony, Amgen's amendment would be understood by those skilled in the art to encompass EPO with a 165-amino-acid sequence. App. 329a-334a. Accordingly, "it would not be reasonable to expect Amgen to have drafted the claim differently." App. 331a.

E. The Federal Circuit's Panel Decision

1. a. Applying *de novo* review, and disregarding the district court's findings, the panel majority attempted, in four scant pages, to construe the claim term "therapeutically effective amount" from scratch. App. 12a-16a.

First, the panel returned to the portion of the specification quoted on page 6, *supra*, and found that it "supports the construction that the '422 patent encompasses a pharmaceutical composition which produces 'any or all' of the * * * listed effects," as opposed to an amount that produces any of those effects *and* treats or heals. App. 13a-14a. Second, the majority

sua sponte focused on another section of the specification, one dealing with protein "fragments duplicating only a part of" the full EPO sequence. These, the specification explains, "may possess one activity of EPO (e.g., receptor binding) and not others (e.g., erythropoietic activity). * * * [T]he absence of in vivo activity for any one or more of the 'EPO products' of the invention is not wholly preclusive of therapeutic utility (see, Weiland et al., supra)." '422 patent col. 36.[4] To the majority, this passage meant that "'therapeutic utility' is not dependent on the product having an effect in a living being." App. 15a. The majority then decreed that "the patentee used the words 'therapeutically effective' in order to broadly claim a pharmaceutical composition with a wide range of effects" that "do not *necessarily* include curing disease in humans." *Ibid.* Having redefined the claim, the panel again remanded for a finding whether the claim was anticipated by the Goldwasser study and therefore invalid under 35 U.S.C. § 102. App. 18a-19a.

b. Chief Judge Michel dissented, expressing "strong disagreement." He praised Judge Young's "meticulous attention" to the case and called his performance "a model for all trial courts." App. 43a-44a. Judge Michel agreed with the district court's analysis of the specification and prosecution history, and thought the district court "correctly recognized that merely eliciting a biological effect is not the same as being therapeutically effective." App. 44a. Judge Michel observed that the district court's construction "comports with the patentee's own repeated descriptions of the claimed invention. It is exactly the

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[4] The cited Weiland study, which the majority gave no indication of having read, showed that a relative of EPO, despite producing no in vivo effects by itself, induced red blood cell generation *when combined with another substance.* E. Weiland et al., *In Vivo Activity of Asialo-Erythropoietin in Combination with Asialo-Glycoproteins*, 44 BLUT 173 (1982). Hence, just as the patent said, the absence of in vivo effects from an EPO relative does not wholly preclude its potential use in therapy – which is not the same as saying that the relative on its own produces a therapeutically effective result.

way a skilled artisan would interpret the patent." App. 49a. Finally, he criticized the majority for prolonging litigation that "has already dragged on for almost ten years." App. 50a.

2. The court of appeals also reversed Judge Young's *Festo* ruling. App. 33a-40a. At oral argument, respondents conceded that, to the extent factual findings undergird a determination that the presumption of estoppel has been rebutted, they should be reviewed for clear error. In its opinion, however, the panel followed circuit precedent characterizing the estoppel inquiry as a question of law to be reviewed *de novo*. App. 33a. On the second *Festo* criterion, the panel disagreed that the rationale for amendment was tangential to the equivalent, because the addition of the Figure 6 reference "may have been central to overcoming a double patenting rejection," App. 37a. On the third criterion, the panel said that, even if (as Judge Young found) "the patentee, the examiner, or a person of skill in the art [would] have thought the claims encompassed EPO with 165 amino acids," that would "not excuse the patentee's failure to claim the equivalent. * * * [T]here was no linguistic barrier to claiming EPO comprised of 165 amino acids." App. 39a.

F. The Opinions Dissenting from and Concurring in the Denial of Rehearing En Banc

Amgen's petition for rehearing was denied but provoked six opinions in which four judges squarely criticized *de novo* review of claim constructions, three judges criticized limited aspects of the practice, and at least five judges disagreed with the panel majority's claim construction.

Chief Judge Michel's dissent questioned the rule of *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc), that all aspects of a claim construction are reviewed *de novo*. He disputed *Cybor*'s "premise that claim construction is always a purely legal exercise, devoid of factual content":

> [T]he claim construction question often cannot be answered without assessing, at least implicitly, what the average artisan knew and how she thought about the particular technology when the patent claims were written.

> To make such determinations, the trial judge necessarily relies upon * * * evidence concerning the skill of the ordinary artisan at the relevant time. Indeed, trial judges are arguably better equipped than appellate judges to make these factual determinations, especially in close cases.

App. 596a-597. Judge Michel observed (App. 596a) that "four practical problems have emerged under" the *Cybor* regime:

> (1) a steadily high reversal rate; (2) a lack of predictability about appellate outcomes, which may confound trial judges and discourage settlements; (3) loss of the comparative advantage often enjoyed by the district judges who heard or read all of the evidence * * *; and (4) inundation of our court with the minutia of * * * disputed claim terms * * * in nearly every patent case.

Judge Rader's dissent also criticized *Cybor* and urged "deference to the factual components of the lower court's claim construction." App. 604a. "As is often the case," he explained, "the district court was better positioned * * * to reach the proper construction" because it "has more tools, more time, and more direct contact with factual evidence." *Ibid.* The trial court had heard testimony from "artisans informed of the meaning of 'therapeutically effective amount' at the time of invention," and Judge Rader found it significant that Judge Young, while disclaiming reliance on expert testimony, specifically noted that that testimony fully supported his claim construction. Given the Federal Circuit's rules discouraging resort to extrinsic evidence, Judge Rader remarked, "district court judges have learned to disclaim any reliance on expert testimony." App. 605a.

Judge Newman's dissent argued that the *de novo* standard "has not well withstood the test of experience." App. 601a. In her view (*ibid.*):

> [F]indings of science/technology-based facts in patent cases should receive appellate review on the same basis as other science-based findings * * *. The [Supreme] Court's and our own precedent require the trial judge to evaluate

> scientific evidence and expertise from the viewpoint of a person experienced in the field of science, a framework that aptly fits evaluation of the * * * scope of patents * * *.

Judge Newman also criticized the panel majority for broadening the claim when the PTO allowed the patent only because Dr. Lin distinguished his invention on the basis of its ability to heal or cure. App. 599a-600a. Judge Lourie, too, thought the panel majority had "incorrectly construed" the claim, but believed that the case did not merit en banc review. App. 603a.

Judge Gajarsa, joined by Judges Linn and Dyk, concurred. They did not endorse the panel's construction but were willing to reconsider only "limited aspects" of *Cybor*, namely the standard of review in "the atypical case" in which the claims, specification, and prosecution history "on their face did not resolve the question of claim interpretation, and the district court found it necessary to resolve conflicting expert evidence." Here, Judge Young "disavowed reliance on extrinsic expert evidence." The concurring judges believed that "[n]o deference is due a district court's legal interpretation of the claim language, written description, and prosecution history," because "an appellate court is equally competent to interpret" those materials. App. 606a-607a.

Judge Moore dissented. She praised Judge Young's efforts, criticized the lack of deference to them, and called for reconsideration of *Cybor*. Judge Moore, like Judge Rader, also found it significant that the district court "explain[ed] that the claim construction is supported by the expert testimony" but said that such testimony was being used only to "'understand the technology'" and not to "'define the term.'" App. 608a-609a.

REASONS FOR GRANTING THE PETITION

Plenary *de novo* review of claim construction does not work. It produces incorrect results and causes litigants and district courts to waste tremendous resources. The practice, which has been savaged by a sizable minority of the Federal Circuit, rests on the false premise that claim construction entails no factual inquiry. Construction of patent claims

depends on technological mastery and is therefore, like the inquiry into the reliability of scientific testimony under *Daubert* v. *Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), something for which trial courts are uniquely suited and owed special deference. The Federal Circuit's simplistic syllogism – if an issue is for the court, it must be subject to complete *de novo* review on appeal – flies in the face of Rule 52(a) and is belied by well-established practice in patent and other areas of the law in which the factual determinations undergirding a court's legal pronouncement are reviewed for clear error.

This case exemplifies the perils of *de novo* review. The district court's determination was a product of acquired familiarity with a technical discipline. In the face of specification language that associated certain biological effects with "use in therapy procedures," the judge, drawing on all he had read, heard, and seen, concluded that one of skill in the art would not understand, and the PTO did not understand, that passage to define each of those effects as itself "therapeutically effective." But the panel, presuming to read the specification more competently than the district judge or the PTO, gave the passage in question a meaning contrary to the understanding in the field, and focused on – and flatly misunderstood – a different portion of the specification, one that neither the parties nor the district court had thought relevant in a decade of litigation. This Court's review is necessary to curb this type of overreaching and bring the Federal Circuit's approach to factual issues in line with that of other appellate courts.

The Federal Circuit's treatment of Judge Young's prosecution history estoppel ruling also raises important and recurring issues. Again without the benefit of the district court's special familiarity, the court of appeals failed to focus, as this Court has instructed, on the rationales for amendment and the reasonableness of the drafting. Instead the panel used *de novo* review to convert the former inquiry into an insurmountable tautology and the latter into a redundancy with a foreseeability test so narrow that it has never been satisfied. The decision strips both *Festo* and *Warner-Jenkinson* of real meaning, in

practice resurrecting the complete bar to a claim against equivalents for an amended patent that was rejected in those cases.

I. This Court Should Review The Federal Circuit's Much-Criticized View That It Owes No Deference To District Court Claim Constructions

The *de novo* standard of review, as applied indiscriminately to facts and technical mastery underlying claim construction, is a power grab by the Federal Circuit at the expense of the district courts and the judicial process. The standard, adhered to in three en banc decisions despite vociferous opposition from a substantial minority of the Federal Circuit[5] and criticism from the bench, bar, and beyond,[6] is overdue for further review.

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[5] In addition to the dissents from denial of rehearing in this case, see, *e.g.*, *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1330, 1334-35 (Fed. Cir. 2005) (en banc) (Mayer, J., dissenting) ("Now more than ever I am convinced of the futility, indeed the absurdity, of * * * adhering to the falsehood that claim construction is a matter of law devoid of any factual component."); *Cybor*, 138 F.3d at 1478 (Rader, J., dissenting) ("[T]his court misses the opportunity to improve certainty in patent practice by giving appropriate deference to trial court claim interpretations."); *Cybor*, 138 F.3d at 1480 (Newman, J., additional views) ("By continuing the fiction that there are no facts to be found in claim interpretation, we confound rather than ease the litigation process.").

[6] See, *e.g.*, Johnson, *The False Premise and Promises of* Markman *'s Decision To Task Judges with Claim Construction and the Judicial Scorecard*, Practising Law Institute (2005); Burgess, Comment, *Simplicity at the Cost of Clarity: Appellate Review of Claim Construction and the Failed Promise of* Cybor, 153 U. PA. L. REV. 763 (2004); Rooklidge & Weil, *Judicial Hyperactivity: The Federal Circuit's Discomfort with Its Appellate Role*, 15 BERKELEY TECH. L.J. 725 (2000); Am. Bar Ass'n *Amicus* Br., *Phillips* v. *AWH Corp.*, No. 03-1269, at 17-21, 2004 U.S. Fed. Cir. Briefs LEXIS 32 (Fed. Cir. Sept. 20, 2004); Fed. Cir. Bar Ass'n *Amicus* Br., *Phillips*, at 7-9; *Lucas Aerospace, Ltd.* v. *Unison Indus., L.P.*, 890 F. Supp. 329, 333 n.7 (D. Del. 1995) ("[W]hen the Federal Circuit * * * states that the trial court does not do something that the trial court does and must do to perform the judicial function, that court knowingly enters a land of sophistry and fiction.").

A. Claim Construction Entails Factual Inquiry, And This Case Is No Exception

1. The Federal Circuit held in *Markman* v. *Westview Instruments, Inc.*, 52 F.3d 967, 970-971, 981 (Fed. Cir. 1995) (en banc) ("*Markman I*"), aff'd on other grounds, 517 U.S. 370 (1996) ("*Markman II*"), that "the interpretation and construction of patent claims * * * is a matter of law exclusively for the Court." The Federal Circuit also asserted that claim construction entails no factfinding even though it depends on evidence (52 F.3d at 981): "By * * * using certain extrinsic evidence that the court finds helpful and resolving disputes en route to pronouncing the meaning of claim language * * * based on the patent documents themselves, the court is *not* crediting certain evidence over other evidence or making factual * * * findings."

Markman II agreed that claim construction is for the court, but pointedly did not agree that it is a purely legal endeavor. On the contrary, this Court characterized "construing a term of art following receipt of evidence" as a "mongrel practice" and recognized that "credibility judgments have to be made about the experts who testify in patent cases," but held that *trial* judges are "better suited" than juries to this activity because judges are trained "to evaluate the *testimony* in relation to the overall structure of the patent." 517 U.S. at 378, 389-390 (emphasis added). Accordingly, "there is sufficient reason to treat construction of terms of art like many other responsibilities that we cede to a judge in the normal course of trial, notwithstanding its *evidentiary underpinnings*." *Id.* at 390 (emphasis added). This Court, moreover, said nothing about the standard of appellate review of a judge's claim construction.

But the en banc Federal Circuit saw in *Markman II* what it wanted to see, and announced that the decision authorized it to "review claim construction *de novo* on appeal including any *allegedly fact-based questions*." *Cybor*, 138 F.3d at 1456 (emphasis added). That ruling is here to stay. Three years ago, the Federal Circuit invited briefing on whether "consistent with" *Markman II* and *Cybor* – in other words, *without*

reconsidering *Cybor* – the court of appeals owed "any deference to any aspect of trial court claim construction rulings." Even that question the court simply "decided not to address." *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1328 (Fed. Cir. 2005) (en banc), cert. denied, 126 S. Ct. 1332 (2006). And, again in this case, the en banc court showed no interest in reconsidering *Cybor*'s core holding.

2. Patents are written for those skilled in the art to which they pertain, *e.g.*, *W.L. Gore & Assocs., Inc.* v. *Garlock, Inc.*, 721 F.2d 1540, 1556 (Fed. Cir. 1983); 35 U.S.C. § 112, and so claim language must be interpreted "as one of skill in the art at the time of invention would understand" it. *Eastman Kodak Co.* v. *Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1555 (Fed. Cir. 1997). The trial court thus must determine: the state of the art as of the date of the invention; what the claim, in light of the specification, would mean to one of skill in the art; and what one of skill would understand from the statements the applicant made to the PTO to distinguish his invention from the prior art.

These are fundamentally assessments of fact, not law; they depend – as this Court acknowledged in *Markman II* – on *evidence*. See, *e.g.*, *Bayer AG* v. *Biovail Corp.*, 279 F.3d 1340, 1349 (Fed. Cir. 2002) ("[I]t would be premature for this court to engage in its own claim construction without * * * *evidence of the meaning of the terms* to one of skill in the art at the time of invention.") (emphasis added); see also *Markman I*, 52 F.3d at 999 (Newman, J., dissenting) ("[T]he meaning and scope of disputed technologic and other terms of art * * * are classic[] questions of fact.").[7] This Court also said as much in the

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[7] Judge Mayer's description of a *Markman* hearing is particularly revealing (*Phillips*, 415 F.3d at 1332 (dissenting opinion)):

> [P]arties battle over experts offering conflicting evidence regarding who qualifies as one of ordinary skill in the art; the meaning of patent terms to that person; the state of the art at the time of the invention; contradictory dictionary definitions and which would be consulted by the skilled artisan; the scope of specialized terms; the problem a patent was solving; what is related or pertinent art; * * *

context of obviousness under 35 U.S.C. § 103, when it labeled the following inquiries – which are similar to those necessary for claim construction – as factual: "the scope and content of the prior art," "differences between the prior art and the claims at issue," and "the level of ordinary skill in the pertinent art." *Graham* v. *John Deere Co.*, 383 U.S. 1, 17 (1966).

3. The Federal Circuit's mischaracterization of claim construction is responsible for what Judge Young called a "conundrum." App. 77a n.23. The Federal Circuit recognizes that expert testimony, dictionaries, and treatises "may be helpful to explain scientific principles, the meaning of technical terms, and terms of art that appear in the patent and prosecution history," and the state of the art at the time of the invention. *Markman I*, 52 F.3d at 980. But at the same time the court discourages district courts from relying on this extrinsic evidence. See, *e.g.*, *Phillips*, 415 F.3d at 1319; *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996). As Judge Young wondered: "How does a Court decipher the plain and customary meaning of a term as understood by one skilled in the art without resorting to extrinsic evidence about how one skilled in the art would construe the term?" App. 77a n.23. That paradox, acknowledged by Judges Rader and Moore in dissent below,[8] see pages 12-13, *supra*, is only enhanced when the Fed-

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> how one of skill in the art would understand statements during prosecution; and on and on. * * * [T]he district court is required to sift through and weigh volumes of evidence.

[8] Judge Rader also commented on this difficulty in *Cybor*, 138 F.3d at 1474-1475 (dissenting opinion) (citation omitted):

> [T]his court instructs experienced trial judges that they may use experts to understand, but not to interpret, the claim terms. As a matter of logic, this instruction is difficult to grasp. * * * [A] trial court must often resort to experts to learn complex new technologies. What happens when that learning influences a trial judge's interpretation of the claim terms? Are trial judges supposed to disguise the real reasons for their interpretation? How will this perverse incentive to "hide the ball" improve appellate review?

eral Circuit applies *de novo* review to constructions crucially informed by the very extrinsic sources to which the district court has superior access. The Federal Circuit tends, just as it did here, to ignore the extrinsic sources, see Dobrusin, *Post-Cybor: Can Past Performance Dictate Future Practice?*, IP LITIGATOR, Sept.-Oct. 1998, at 9-10 (Aspen Law & Business), and so its constructions are inevitably less accurate than those of the district court.

This is one of several reasons why Judge Gajarsa's concurrence in denial of rehearing is wide of the mark.[9] Judge Gajarsa took issue only with the periphery of *Cybor*, not its core, saying he would reconsider *Cybor* only to the extent that a district court has had to resolve *conflicting expert testimony*. But *Cybor*'s core is rotten, too: *all* claim constructions deserve at least some deference. Patents can be understood only with reference to technology, and the district judge who has immersed himself in that technology and its terminology – including by listening (as Judge Young did) to *non-conflicting* experts[10] – is in the best position to construe the patent.

Indeed, this case is an object lesson on the importance of deference. By the time he construed "therapeutically effective," Judge Young had received tutorials from an M.I.T. scientist, listened to 32 days of testimony from 35 scientists, and read countless pages of written submissions. His claim construction opinion repeatedly emphasized that his analysis was supported by his familiarity with the technology and the testimony of the parties' concurring scientific experts, which gave him key insights into – among many other things – the clinical significance of different signs of red blood cell generation.

For instance, after using dictionaries to establish a working assumption about the meaning of "therapeutically effective amount," Judge Young turned – as Federal Circuit precedent demands – to the language of the claims, his analysis of which

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[9] Another is discussed at page 22, *infra*.

[10] See page 8, *supra*.

was based on "a careful review of the technology and its history" that "relied on extrinsic evidence." Judge Young observed that, "[w]hile the Court cannot rely on expert testimony to help construe the term * * * unless absolutely necessary, it may look to the expert testimony to better understand the technology." He emphasized that his conclusions were informed by his "understanding of the technology," namely, his knowledge of the state of the art before Amgen's invention and the nature of Amgen's contribution. App. 84a-86a & n.28.

The same was true of Judge Young's reading of the specification. His task, as a matter of Federal Circuit precedent and especially in light of the first panel opinion, was to determine whether the specification, *read from the standpoint of one skilled in the art*, redefined "therapeutically effective" to require only certain biological effects besides an increase in hematocrit. In answering in the negative, he specifically noted that his reading "comports with the Court's understanding – developed over the course of two intensive trials – of what hematocrit actually measures. * * * [I]n *most* cases, an increase in hematocrit is accompanied, if not preceded, by 'any or all' of the biological effects listed in the specification." App. 91a.

Finally, Judge Young's analysis of the prosecution history for purposes of claim construction also drew on his intimate familiarity with this case. He explained that Amgen, to overcome rejections in the PTO, "differentiated its product from natural EPO * * * by asserting that natural EPO – which elicits the biological effects – was not therapeutically viable, whereas its product was clinically effective." App. 101a. Judge Young pointed out as well that the patent examiner must be presumed to have done his job, and that, "'if he truly thought that' Amgen's EPO" merely elicited the same effects as natural EPO, he would not have allowed the patent. App. 109a.

Judge Young thus understood, and the panel majority clearly did not, that *to skilled practitioners* numerous biological effects (an increase in the number of immature red blood cells,

for example) signal an increase in red blood cell production without *on their own* amounting to an increase in the total level of mature red blood cells. These effects, rather, are necessary precursors of the clinically useful result – the increase in hematocrit – which may or may not follow. In other words, the early indicators of red blood cell generation are necessary, but not sufficient, to treat anemia. Judge Young further understood that earlier EPO compositions, despite having reportedly induced some biological changes, were too impotent to increase hematocrit, which is how Amgen distinguished its product from the prior art in the first place. Armed with that knowledge, Judge Young concluded that, even though the specification associated certain biological changes with "therapy procedures," it would never occur to *a skilled practitioner reading the specification* that (as the panel majority thought) an amount *merely* eliciting one of these changes would be a "therapeutically effective amount." This was a factual determination, and it deserved deference.

4. Claim constructions should be reviewed in the same way as other conclusions entrusted to a judge but based on factual determinations. For example, validity under the nonobviousness standard of 35 U.S.C. § 103, though ultimately a question of law, rests on "several basic factual inquiries" akin to the inquiries underlying claim construction. See *Graham*, 383 U.S. at 17; pages 17-18, *supra*. Those inquires, under Rule 52(a), are reviewed only for clear error. *Dennison Mfg. Co.* v. *Panduit Corp.*, 475 U.S. 809 (1986). Similarly, under the Uniform Commercial Code, when a contract contains "usage of trade" terminology, "the existence and scope of such a usage are to be proved as facts," U.C.C. § 1-205, which are then reviewed for clear error. *E.g.*, *Voest-Alpine Trading USA Corp.* v. *Bank of China*, 288 F.3d 262, 265 (5th Cir. 2002). The law abounds with other examples of deferential appellate review of the facts undergirding a legal conclusion. See, *e.g.*, *Ornelas* v. *United States*, 517 U.S. 690, 699 (1996) (facts underlying judge's determination of probable cause are reviewed for clear error); *United States* v. *Bajakajian*, 524 U.S. 321, 337 n.10 (1998)

(same for factual findings made in inquiring into excessiveness of a fine). Claim constructions should be treated the same way.

Nor should the standard of review depend, as Judge Gajarsa's concurrence suggested, on whether the district court's claim construction makes use of live testimony. There is no reason to believe that when this Court acknowledged the "evidentiary underpinnings" of claim construction, *Markman II*, 517 U.S. at 390, it had only extrinsic evidence in mind. The patent and, especially, its prosecution history – though documentary in nature – are still *evidence* from which a tribunal must make case-specific findings, not just announce principles of law. And it is settled that federal judges' factual findings are reviewed for clear error even when based only on documentary evidence. FED. R. CIV. P. 52(a); *Anderson* v. *Bessemer City*, 470 U.S. 564, 574 (1985).

B. District Courts Are Institutionally "Better Positioned" Than Appellate Courts To Construe Patent Claims

Markman II was based on "'a determination that, as a matter of the sound administration of justice,'" a judge is "'better positioned'" than a jury to construe patent claims, 517 U.S. at 388. Similarly, the standard of appellate review "should depend upon 'the respective institutional advantages of trial and appellate courts.'" *First Options of Chicago, Inc.* v. *Kaplan*, 514 U.S. 938, 948 (1995); see also *Cooter & Gell* v. *Hartmarx Corp.*, 496 U.S. 384, 402-404 (1990); *Pierce* v. *Underwood*, 487 U.S. 552, 559-560 (1988). In claim construction, there can be no question where the advantage lies, for district judges have superior tools for educating themselves on technology. They can question the parties' experts, appoint their own experts, receive tutorials from scientists, call for whatever submissions are necessary, and even conduct on-site visits (see *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 611 (1950)).

This Court has expressed firm confidence in district judges' ability to handle complex technical issues. *Daubert* v. *Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), instructs district judges to ascertain the reliability of expert

testimony, even though that sometimes requires them "to make subtle and sophisticated determinations about scientific methodology," *General Electric Co.* v. *Joiner*, 522 U.S. 136, 147 (1997) (Breyer, J., concurring).[11] This Court nevertheless said it was "confident that federal [district] judges possess the capacity to undertake this review." 509 U.S. at 593. The *Markman* procedure in many ways is analogous to the *Daubert* procedure – both require a judge to assimilate and evaluate technical information. But, whereas *Daubert*'s vote of confidence culminated in *Joiner* – which held that a *Daubert* decision is reviewed only for abuse of discretion, 522 U.S. at 146 – the Federal Circuit substitutes its judgment for that of the district court in every case in which *de novo* review prompts two appellate judges to reach a different conclusion.

In *Markman I*, the Federal Circuit analogized claim construction to statutory construction, 52 F.3d at 987, apparently believing, as Judge Gajarsa's concurrence asserts, that trial and appellate courts are "equally competent" to interpret patent documents. App. 607a. That analogy is not only questionable under Rule 52(a) and *Anderson* v. *Bessemer City*, *supra* – which require appellate deference to factual findings based purely on documentary evidence – but flawed on its own terms. As Chief Judge Michel's dissent from denial of rehearing explains, appellate judges, as "artisans in the law," may indeed be equally competent to construe a statute but are at a distinct disadvantage when it comes to putting themselves in the position of one of ordinary skill in a scientific or technical discipline. App. 596a.

A compelling illustration of this point is the panel majority's performance in this very case. The majority failed to grasp

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[11] Justice Breyer commented approvingly in *Joiner* on the use of technical advisors and special masters to help make determinations about "complicated scientific, or otherwise technical, evidence." 522 U.S. at 149. Judge Young – unlike the panel – benefited from both a technical advisor and a special master. See pages 5 and 7, *supra*.

basic concepts like what hematocrit measures,[12] radically misread the specification, and then gave the claims a naïvely broad meaning that ignored the precise features that distinguished the invention from what was already known. The majority did not appreciate that, *from the standpoint of a skilled practitioner*, Dr. Lin's discussion of biological effects in connection with "therapy procedures" would not convert each of those effects into a "therapeutically effective" result. Saying that something is "suitable for use in erythropoietin therapy procedures * * * to develop * * * effects here[to]fore attributed to" EPO is not at all the same thing as saying that merely producing one of those effects is equivalent to therapeutic effectiveness. It is to avoid just this sort of mistake, made by appellate judges who cannot possibly learn the technology as deeply as an able trial judge, that deference is "particularly" called for when "so much depends upon familiarity with specific scientific problems and principles." *Graver Tank*, 339 U.S. at 610.

The panel was even more confused about the passage it raised *sua sponte*, which said that various EPO fragments or relatives that are *not* the subject of the claim at issue can have "therapeutic utility" even if they produce no in vivo effects on their own. The majority, apparently without consulting the citation in the passage, see note 4, *supra*, and overlooking the fact that "therapeutic utility" and "therapeutically effective" are different terms, believed this was evidence that the patentee "did not use the word 'therapy' in order to limit the scope of the '422 patent to only EPO that cured disease," App. 15a – even though that is a total non sequitur and ignores the *majority*'s notion that "therapeutic effectiveness" is equivalent to the in vivo effects. Errors like this are inevitable when appellate courts, which do not have the benefit of all the submissions and testimony available to the district court, embark on their own factfinding.

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[12] The majority thought hematocrit is the "ratio of red blood cells to total blood cells." App. 5a. Hematocrit is rather the ratio of red blood cell *volume* to total blood *volume* – not at all the same thing.

C. This Issue Has Paramount Importance For Patent Litigation And Is Ripe For Review By This Court

This case readily qualifies for further review. Not only is the Federal Circuit profoundly and irreconcilably divided, a circumstance that in the past has prompted review in this Court,[13] but the question presented is surpassingly important. *De novo* review misallocates judicial resources, spawns needless disputes, prolongs litigation, and destroys certainty.

De novo review misallocates judicial resources because appellate courts usually cannot replicate the factual understanding of the district courts, see *Pierce*, 487 U.S. at 560, which may be why more than one-third of claim constructions are being reversed on appeal.[14] This enormous reversal rate confounds and demoralizes district judges.[15] Moreover, as this case highlights, an appellate do-over wastes the often-large investment in the trial judge's education. See, *e.g.*, Lueders et al., *Refining* Cybor, INTELL. PROP. TODAY, Nov. 2006, at 17, 18. It is precisely to avoid problems like this that Rule 52(a) mandates deference even to documentary-based findings. See Rule 52 Adv. Comm. notes ("To permit courts of appeals to share more actively in the fact-finding function would tend to undermine the legitimacy of the district courts in the eyes of litigants, multiply appeals by encouraging appellate retrial of

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[13] See *Warner-Jenkinson*, 520 U.S. at 21 (review warranted given "[t]he significant disagreement within the * * * Federal Circuit"); see also *Festo*, 535 U.S. at 730 (four judges in four opinions dissented from en banc decision); *Cardinal Chem. Co.* v. *Morton Int'l, Inc.*, 508 U.S. 83, 88 (1993) (three dissents from denial of rehearing en banc).

[14] Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 LEWIS & CLARK L. REV. 231, 233 (2005).

[15] See *A Panel Discussion: Claim Construction from the Perspective of the District Judge*, 54 CASE W. RES. L. REV. 671, 672 (2004) ("[S]ometimes we think that the only thing that really is predictable in this area of the law is that we district judges will likely get it wrong, or at least that the Federal Circuit will say that we got it wrong.").

some factual issues, and needlessly reallocate judicial authority.").

De novo review also makes litigation exceptionally costly for the parties. Definitive claim constructions tend to promote settlement: "Once the parties know the meaning of the claims, they can predict with some reliability the likelihood of a favorable judgment, factor in the economics of the infringement, and arrive at a settlement to save the costs of litigation." *Cybor*, 138 F.3d at 1475 (Rader, J., dissenting). But when every claim construction is revisited *de novo* in the Federal Circuit – where the odds of reversal are huge and a "sporting element" is created by "unexpectedly creative de novo claim interpretations," *Cybor*, 138 F.3d at 1479 (Newman, J., additional views) – prediction becomes impossible until after the appeal is decided. What is more, at that point a whole new trial under a new claim construction may be necessary, just as it is in this case. Finally, the current regime creates an incentive to contest every possible claim term, hoping that at least one argument might succeed on appeal. See *Cybor*, 138 F.3d 1476 (Rader, J., dissenting) ("As the focus shifts * * * to preserving ways to compel reversal on appeal, the uncertainty, cost, and duration of patent litigation only increase."). Here, for example, "therapeutically effective," though not even on the list of the top ten disputed terms for the first *Markman* hearing, see App. 430a, remains in dispute a decade after this litigation began.

II. This Court Should Review The Federal Circuit's Near Abolition Of The Doctrine Of Equivalents In Any Case In Which A Patent Has Been Amended

This Court has long recognized that patent protection would be meaningless if an imitator could circumvent a patent by making "unimportant and insubstantial changes and substitutions" to the invention. *Graver Tank*, 339 U.S. at 607 (citing *Winans* v. *Denmead*, 56 U.S. (15 How.) 330 (1854)). Just as Judge Young found with respect to the single amino acid discrepancy at issue here, "[t]he language in the patent claims may not capture every nuance of the invention or describe with

complete precision the range of its novelty." *Festo*, 535 U.S. at 731. Accordingly, "[t]he scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims." *Id.* at 732. At the same time, this Court has recognized that the doctrine of equivalents is in tension with the public notice function of patents. *Ibid.* However, rather than accept repeated invitations to "speak the death" of the doctrine, *Warner-Jenkinson*, 520 U.S. at 21, the Court has endeavored to reconcile the competing interests. Thus *Festo* clarified that a narrowing amendment to a patent claim during prosecution presumptively surrenders equivalents to the amended claim that would have been literally covered by the unamended version.

The rebuttability of this presumption is essential. *Warner-Jenkinson* rejected a "rigid rule invoking an estoppel regardless of the reasons for" amendment. 520 U.S. at 32. And *Festo* reversed a highly formalistic Federal Circuit decision holding that prosecution history estoppel is a complete bar to a claim of infringement by equivalents. *Festo* explained that the bar should not apply when "the amendment cannot reasonably be viewed as surrendering a particular equivalent," as when (1) the equivalent was "unforeseeable at the time of the application"; (2) "the rationale underlying the amendment * * * bear[s] no more than a tangential relation to the equivalent in question"; or (3) "some other reason suggest[s] that the patentee could not reasonably be expected to have described the insubstantial substitute in question." 535 U.S. at 740-741. Yet the Federal Circuit has been virtually heedless of these pronouncements.

A. The most significant of the three *Festo* criteria is the second, which deals with the relationship between the rationale for amendment and the equivalent at issue. The court of appeals' entire reasoning under this criterion is contained in this non sequitur: "[T]he [reference to the Figure 6 sequence] added in the * * * amendment may have been central to overcoming a double patenting rejection in light of claim 1 of the '933 patent. Under these circumstances we cannot say that the reason for the [amendment] was merely tangential to the alleged 165-amino acid equivalent." App. 37a-38a. But it was already

established that the amendment was designed to avoid a double-patenting rejection. The question under *Festo* is rather whether that *reason* – the need to avoid duplication – has any significant relationship to the distinction between 165 and 166 amino acids. As Judge Young determined – after careful examination of the prosecution history informed by technical conversance that the court of appeals lacked – it does not. App. 318a-323a. The amendment simply was not made to distinguish a polypeptide having 165 amino acids from one having 166.

In focusing on the *result* of the amendment rather than its purpose, the court of appeals erected a roadblock across the most important avenue for avoiding estoppel. As Judge Young explained when TKT committed the same fallacy in the district court, this mode of analysis conflates two things: (1) the relationship between the reason for the amendment and issues of patentability, and (2) the relationship between the reason for amendment and the equivalent in question. The rationale for amendment "cannot be more than tangentially related to" the equivalent in question, "but it *can* be more than tangentially related to patentability issues" – after all, it is because of the relationship to patentability that the presumption of estoppel arises in the first place. In ruling to the contrary, the court of appeals made this crucial standard "circular and insurmountable." App. 323a. More recently, the Federal Circuit has held "that the tangential relation criterion for overcoming the *Festo* presumption is very narrow" and vacated yet another district court decision accepting a rebuttal case under that criterion. *Cross Med. Prods., Inc.* v. *Medtronic Sofamor Danek, Inc.*, No. 05-1415, 2007 WL 817660, at *5 (Fed. Cir. Mar. 20, 2007).

The Federal Circuit also destroyed the residual *Festo* criterion dealing with whether the patentee could "reasonably be expected to have described" the equivalent. Judge Young found that the patentee, the examiner, and a hypothetical person of skill in the art all understood the amended claim to encompass a 165-amino-acid polypeptide. "It is not reasonable to expect * * * different claim language when the language that was used was interpreted by those skilled in the art to be sufficiently de-

scriptive." App. 333a. And yet the panel reversed because there was no "linguistic barrier" to claiming the equivalent.

But that is not the issue. As Judge Young explained: "If the question was merely whether the patentee *could* have drafted a claim to encompass the equivalent then the test would simply be a foreseeability test," and there would have been no need for other *Festo* criteria. App. 295 n.13. The whole point of the residual criterion is to "soften[] the harsh standard that may be inherent in the foreseeability test. After all, it may be *unreasonable* to require the patentee to exhaust every arguably foreseeable equivalent in the world." Fu, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 18 BERKELEY TECH. L.J. 117, 137 (2003) (emphasis added). Indeed, the foreseeability standard has not succeeded in one appellate decision since *Festo*. Thus the court of appeals has collapsed the *Festo* criteria into ones with no practical application, effectively reviving the complete-bar rule this Court rejected in *Festo*.

B. Moreover, the court of appeals' aggressive disregard for Judge Young's prosecution history estoppel rulings is of a piece with its disdain for trial court claim constructions. As Judge Young pointed out (App. 292a n.11), treating a finding on prosecution history estoppel as a pure question of law reviewable *de novo* on appeal has deleterious consequences comparable to those in the claim construction context.

Festo contemplated that a patentee could "show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." 535 U.S. at 741. Because the prosecution history and specification alone cannot possibly permit such a demonstration, this Court clearly was calling for an inquiry into factual and technological circumstances. The en banc Federal Circuit even acknowledged on remand from *Festo* that "rebuttal of the presumption may be subject to underlying facts." *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1368 n.3 (Fed. Cir. 2003). Sure enough, Judge Young's decision was informed by

his technical familiarity and evidence of the understanding of skilled artisans. And even though TKT – which *lost* in the district court – conceded during argument that the factual components of a *Festo* determination deserve deference, the Federal Circuit insists on subjecting *Festo* rulings, including Judge Young's, App. 33a, to indiscriminate *de novo* review.[16] This practice violates bedrock principles of appellate review.[17]

The doctrine of equivalents and prosecution history estoppel have vast importance for patent litigation and prosecution. "Outright and forthright duplication is a * * * very rare type of infringement," *Graver Tank*, 339 U.S. at 607, and so a great deal of patent litigation concerns the doctrine of equivalents. *E.g.*, Teague, *Festo and the Future of the Doctrine of Equivalents*, 3 CHI.-KENT J. INTELL. PROP. 1, 16 (2003). Similarly, the vast majority of patents are amended during prosecution.[18] Indeed, this Court chose to hear *Festo* and *Warner-Jenkinson* in part because these two doctrines define so much of the scope of patent protection and influence so heavily applicants' behavior during the application process. This petition, therefore, raising as it does the question whether the Federal Circuit has adopted through the back door the same rule this Court rejected in *Festo*, presents a question no less important than *Festo* did.

CONCLUSION

The petition for a writ of certiorari should be granted.

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[16] *E.g.*, *Conoco, Inc.* v. *Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1357 (2006); *Rhodia Chimie* v. *PPG Indus. Inc.*, 402 F.3d 1371, 1376 (2005); *Ranbaxy Pharms., Inc.* v. *Apotex, Inc.*, 350 F.3d 1235, 1240 (2003).

[17] The practice also runs counter to the United States' position. On remand in *Festo*, the United States explained that the Federal Circuit "should accord considerable deference to the district court's resolution of" subsidiary questions of fact supporting a *Festo* determination because of the respective advantages of trial and appellate courts. U.S. *Amicus* Br. 6-7, No. 95-1066, 2002 WL 32144415 (Fed. Cir. Nov. 2002).

[18] See, *e.g.*, *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 638 n.3 (Fed. Cir. 2000) (en banc) (Newman, J., dissenting).

Respectfully submitted.

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No. 06-1291

In the Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI APPENDIX VOLUME I OF II

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APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

05-1157

AMGEN INC.,
Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,
Defendants-Appellants.

DECIDED: August 3, 2006

Before MICHEL, *Chief Judge*, CLEVENGER, *Senior Circuit Judge*, and SCHALL, *Circuit Judge*.

Opinion for the court filed by *Circuit Judge* SCHALL.

Dissenting-in-part opinion [p. 43a, *infra*] filed by *Chief Judge* MICHEL.

SCHALL, *Circuit Judge*.

This is a patent case. Amgen, Inc. ("Amgen") is the owner of U.S. Patent Nos. 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,621,080 ("the '080 patent"), 5,756,349 ("the '349 patent"), and 5,955,422 ("the '422 patent"). The patents are directed to recombinant deoxyribonucleic acid ("DNA") technology relating to the production of the hormone erythropoietin ("EPO"). All five patents share a common specification and descend from Application No. 06/561,024 ("the '024 application"), filed on December 13, 1983. In April of 1997, Amgen brought a declaratory

judgment action against Hoechst Marion Roussel, Inc. (now known as Aventis Pharmaceuticals Inc.) ("HMR") and Transkaryotic Therapies, Inc. ("TKT") (collectively, "HMR/TKT") in the United States District Court for the District of Massachusetts, alleging that HMR/TKT's Investigational New Drug Application ("INDA") for an EPO product infringed the five patents. In January of 2001, following a *Markman* hearing, summary judgment proceedings, and a bench trial, the district court issued an opinion in which it: (i) construed the disputed claims; (ii) held the patents not unenforceable; (iii) held the asserted claims of the '080, '349, and '422 patents not invalid and infringed with the exception of claim 7 of the '349 patent, which it found not infringed; (iv) held the asserted claims of the '698 patent not infringed; and (v) held the asserted claims of the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 165-66 (D. Mass. 2001) ("*Amgen I*").

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) ("*Amgen II*"), we affirmed *in toto* the district court's claim construction. We also affirmed (i) the court's determination that none of the patents at issue is unenforceable by reason of inequitable conduct; (ii) its contingent determination that the asserted claims of the '933 patent are invalid under section 112; (iii) its grant of summary judgment that claim 1 of the '422 patent is infringed; (iv) its determination that the '933, '698, '080, and '349 patents are not anticipated by U.S. Patent No. 4,377,513 ("the Sugimoto patent"); and (iv) its determination that claims 1, 3, 4, and 6 of the '349 patent are infringed. *Id.* at 1320.

However, we vacated (i) the district court's determination that the asserted claims of the '933 patent are not infringed; (ii) its determination that Dr. Eugene Goldwasser's clinical study, described in Dr. Goldwasser's grant application entitled "Erythropoietin: Purification, Properties, Biogenesis"

("the Goldwasser reference"), and the Sugimoto patent do not anticipate claim 1 of the '422 patent; (iii) its determination that the Sugimoto patent does not render claim 1 of the '422 patent obvious; (iv) its determination that claims 2-4 of the '080 patent are not invalid and are infringed under the doctrine of equivalents; (v) its determination that the asserted method claims of the '698 patent are not rendered obvious by the Sugimoto patent and are not infringed; and (vi) its determination that the Sugimoto patent does not render claims 1, 3, 4, 6, and 7 of the '349 patent invalid and that claim 7 of the '349 patent is not infringed. *Id.*

We remanded the case to the district court to do the following: (i) construe the term "therapeutically effective amount" in claim 1 of the '422 patent and then determine whether either the Goldwasser reference or the Sugimoto patent anticipates claim 1 or whether the Sugimoto patent renders claim 1 obvious, *id.* at 1354, 1356, 1358; (ii) determine whether the Sugimoto patent renders claims 2-4 of the '080 patent obvious and whether, as far as claims 2-4 are concerned, Amgen can rebut the presumption of the surrender of equivalents and thus assert infringement of those claims under the doctrine of equivalents, *id.* at 1345, 1358; (iii) determine whether the Sugimoto patent renders claims 4-9 of the '698 patent obvious and whether claims 4-9 are infringed, *id.* at 1357, 1358; and (iv) determine whether the Sugimoto patent renders claims 1, 3, 4, 6, and 7 of the '349 patent obvious and whether claim 7 of the '349 patent is infringed, *id.* at 1357, 1358.

The case is now back before us following proceedings on remand in which the district court construed the term "therapeutically effective amount" in claim 1 of the '422 patent and conducted a further bench trial. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202 (D. Mass. 2004) ("*Amgen III Validity & Literal Infringement Judgment*"); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F.

Supp. 2d 126 (D. Mass. 2003) ("*Amgen III Doctrine of Equivalents Judgment*"). Based upon various findings and rulings, the court entered judgment in favor of Amgen as follows: (i) claim 1 of the '422 patent is not invalid, *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 334, 336; (ii) claims 2-4 of the '080 patent are not invalid, *id.* at 336, and Amgen is not estopped from asserting infringement of claims 2-4 under the doctrine of equivalents because it rebutted the presumption of surrender of equivalents, *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 160; (iii) claims 4-9 of the '698 patent are not invalid and are literally infringed, *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 336; (iv) claims 1, 3, 4, 6, and 7 of the '349 patent are not rendered obvious by the Sugimoto patent, *id.* at 325, 336, and claim 7 of the '349 patent is literally infringed, *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 336.

On appeal, HMR/TKT challenges all of the above rulings. Our disposition of the appeal is as follows:

(i) Because we hold that the district court erred in its construction of the term "therapeutically effective amount" in claim 1 of the '422 patent, we vacate the judgment of the district court that claim 1 is not invalid. We remand the case to the district court for a determination as to whether the Goldwasser reference anticipates claim 1 under a revised claim construction. (ii) We reverse the judgment of the district court that HMR/TKT's accused product infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We do so because we hold that the district court erred in ruling that Amgen rebutted the presumption that, during prosecution, it surrendered coverage to EPO with a 165-amino acid sequence, which is the sequence of HMR/TKT's product. Because claims 2-4 of the '080 patent are not infringed, it is unnecessary for us to address HMR/TKT's alternative argument by way of an affirmative defense that

claims 2-4 are anticipated by the Goldwasser reference. (iii) We affirm the judgment of the district court that claims 4-9 of the '698 patent are not invalid and are literally infringed. (iv) We affirm the judgment of the district court that claim 7 of the '349 patent is not invalid and is literally infringed. Thus, we affirm-in-part, reverse-in-part, vacate-in-part, and remand.[1]

BACKGROUND

I.

As noted, the patents at issue relate to recombinant DNA technology for the production of EPO. EPO, which is a naturally occurring hormone, stimulates the production of red blood cells in the bone marrow through a process called erythropoiesis. Thus, the production of EPO is useful in treating blood disorders characterized by low hematocrit, which is a low ratio of red blood cells to total blood cells. The production of EPO in usable amounts was made possible by Amgen's team led by Dr. Fu-Kuen Lin, who first successfully identified the EPO DNA sequence. *See* '422 patent, col. 20, ll. 28-33. Amgen markets and sells its EPO product under the brand name "Epogen."

DNA is the genetic material of all living things.[2] *Id.* col. 1, ll. 28-29. DNA is composed of a series of subunits, called nucleotides, that are linked together to form a linear polymeric form—a strand. *Id.* col. 1, ll. 33-35. Each nucleotide contains one of four nitrogen-containing ring compounds, called bases. The bases fall into two categories: pyrimidines,

---

[1] Even though we do not agree with all of the district court's rulings in this case, we note the court's careful and thorough opinions in both *Amgen III Validity & Literal Infringement Judgment* and *Amgen III Doctrine of Equivalents Judgment.*

[2] The basics of recombinant DNA technology are set forth in *Amgen I* and, to a lesser extent, in *Amgen II*. We repeat here only the points necessary for an understanding of the issues presented in this appeal.

which include cytosine ("C") and thymine ("T"), and purines, which include adenine ("A") and guanine ("G"). *Id.* col. 1, ll. 35-46; James D. Watson et al., *Molecular Biology of the Gene* 98 (5th ed. 2004); Bruce Alberts et al., *Molecular Biology of the Cell* 63, 120 (4th ed. 2002). The sequence of A, T, G, and Cs on a strand of DNA forms what is known as a "DNA sequence." DNA is double-stranded, such that two complimentary strands are linked together. '422 patent, col. 1, ll. 35-42.

Genetic information is expressed through the production of proteins, which are molecules containing long chains of amino acids. Alberts, *supra*, at 129. Ribonucleic acid ("RNA") determines the composition of proteins. Watson, *supra*, at 31; *see also* Alberts, *supra*, at 301. During a process called transcription, DNA is used to make messenger RNA ("mRNA") with the sequence corresponding to the DNA sequence of A, T, G, and Cs coding for a particular gene.[3] '422 patent, col. 1, ll. 42-43, 49-51. Transcription of the gene is prompted by a promoter, a sequence of DNA that initiates transcription. *Id.* col. 2, ll. 4-6. The promoter is typically located upstream of the gene to be transcribed.[4] *Id.* After transcription is completed, the mRNA non-coding sequences, called introns, are spliced out and the mRNA coding sequences, called exons, are spliced together. The mRNA sequence is then translated by ribosomes to form a protein

---

[3] As the name "messenger" implies, mRNA transcripts are intermediates in the process of protein synthesis. Transcription of mRNA from DNA is completed in the nucleus of the cell. After it undergoes additional processing in the cell's nucleus, the complete mRNA is exported to the cell's cytoplasm, where it guides the synthesis of proteins. *See* Alberts, *supra* at 304-05, 327-28.

[4] "Upstream" refers to the location of a particular segment of the genetic sequence on a strand of DNA in relation to a particular gene. For example, if a segment is "upstream" of a particular gene and transcription proceeds in a completely linear order along the DNA sequence, then the segment will be transcribed before the gene.

composed of amino acids. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 145.

The common specification of Amgen's patents describes how Dr. Lin combined his discovery of the DNA sequence for EPO with recombinant DNA technology to make EPO-producing cells. In order to create these EPO-producing cells, Dr. Lin made an expression vector carrying the EPO DNA sequence he had discovered. '422 patent, col. 11, ll. 1-10. An expression vector is a circular piece of DNA on which a desired gene may be coded. *See id.* Figs. 2-4, col. 2, ll. 36-54. In addition to the desired gene, an expression vector may also contain a marker and a promoter site. *See id.* col. 3, ll. 35-37, col. 25, ll. 33-36. The expression vector incorporates itself into a host cell's genetic code. The promoter then triggers the host cell to transcribe mRNA corresponding to the genetic code encoded on the vector. *See id.* col. 2, ll. 30-35. This mRNA is then translated into a protein by the host cell. *Id.* The marker in the expression vector enables scientists to identify the cells that successfully incorporated the desired gene. *Id.* col. 25, ll. 64-66. The DNA inserted into the genetic code of the host cell through the expression vector is characterized as exogenous DNA because it is not "native" to the host cell. Genetic recombination using exogenous DNA is referred to as heterologous recombination. *Id.* col. 1, l. 53-col. 2, l. 3.

The expression vector described in Example 10 of the common specification of Amgen's patents contains Dr. Lin's EPO DNA sequence, a selectable dihydrofolate ("DHFR") marker, and a promoter 44 base pairs upstream of the EPO DNA sequence. *Id.* col. 24, l. 17, col. 25, 36-40. When exposed to Chinese hamster ovary ("CHO") cells, Dr. Lin's expression vectors integrate themselves into the DNA of the host CHO cells. *Id.* col. 25, ll. 58-66. The general disclosures in the background section of the '422 patent describe how promoters, like the one used in Example 10, prompt host cells

to transcribe mRNA corresponding to exogenous genes such as the EPO and DHFR genes in Example 10. *See id.* col. 1, ll. 53-56, col. 25, ll. 64-66. In the invention of the five patents, prior to production of a protein from the mRNA with the sequence coding for EPO, the mRNA sequence is spliced to remove introns and to connect exons. After splicing, the mRNA is translated into the 166-amino acid protein shown in Figure 6 of the common specification of the patents.

Prior to secretion from the cell, the 166-amino acid EPO protein undergoes cleaving. In this process, the final amino acid in the sequence shown in Figure 6 of the '422 patent, arginine, is cleaved off, leaving a 165-amino acid protein. This 165-amino acid protein is then secreted as mature human EPO by the cell.

II.

HMR and TKT collaborated to develop a drug known as HMR4396. HMR4396 consists of human EPO produced from TKT's R223 cell line grown in culture. *Amgen I*, 126 F. Supp. 2d at 98. The R223 cell line produces human EPO through the use of a viral promoter that prompts transcription of the human EPO gene. In order to create the R223 cell line, HMR/TKT transfected human tumor cells with the viral promoter. This viral promoter is located far upstream of the EPO gene in the R223 cells. Because the viral promoter is not "native" to the human tumor cells, the R223 promoter is considered exogenous DNA. However, the R223 cells are described as using homologous or endogenous recombination because the human EPO gene that the viral promoter controls is "native" to the cells.

III.

Amgen filed suit for a declaratory judgment that HMR/TKT's HMR4396 infringed the '933 patent, the '698 patent, the '080 patent, the '349 patent, and the '422 patent. Amgen alleged infringement of claims 1, 2, and 9 of the '933 patent,

claims 4-9 of the '698 patent, claims 2-4 of the '080 patent, claims 1, 3, 4, 6, and 7 of the'349 patent, and claim 1 of the '422 patent. *See Amgen I*, 126 F. Supp. 2d at 96-98. The case proceeded as outlined above and is again before us on appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On this appeal, we are presented with issues relating to the '422, '080, '698, and '349 patents.[5] We begin with the '422 patent.

I.

The '422 Patent

Claim 1 is the only claim of the '422 patent at issue in the present case. Claim 1 provides:

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

'422 patent, col. 38, ll. 36-41.

HMR4396 already has been found to infringe claim 1 of the '422 patent. *See Amgen II*, 314 F.3d at 1320. In our remand instructions in *Amgen II*, we instructed the district court to construe the limitation "therapeutically effective amount" in claim 1 and then determine whether the Goldwasser reference or the Sugimoto patent anticipated claim 1 or whether the Sugimoto patent rendered claim 1 obvious.

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[5] As noted above, in *Amgen II*, we affirmed the ruling of the district court in *Amgen I* that claims 1, 2, and 9 of the '933 patent are invalid. *Amgen II*, 314 F.3d at 1342.

A.

Claim Construction

On remand, the district court construed "therapeutically effective amount" in claim 1 of the '422 patent to require that the claimed EPO increase hematocrit *and* also be useful in healing or curing the class of patients listed at column 33, lines 22-28 of the specification of the '422 patent:

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.
>
> Therapeutically effective is to be interpreted as being therapeutically effective with respect to the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 245-46. In arriving at this construction, the district court focused on the portion of the specification of the

'422 patent found at column 33, lines 11-28.[6] *Id.* at 232-36. The court also pointed to statements in the prosecution history asserting that the claimed invention of recombinant human EPO could be used to treat anemia and other similar disorders. *Id.* at 238-42.

On appeal, HMR/TKT contends that the district court erred in construing the term "therapeutically effective" in claim 1 of the '422 patent by requiring that EPO increase hematocrit. HMR/TKT argues that the court incorrectly read the specification as limiting the scope of claim 1 to products that increase hematocrit. HMR/TKT urges that "therapeutically effective amount" means "an amount that elicits any of the biological effects listed in the specification." Under this construction, HMR/TKT asserts, claim 1 is anticipated by the Goldwasser reference.

Amgen responds that the district court correctly interpreted the specification to mean that "when a 'therapeutically effective amount' of EPO is used . . . it produces an increase in hematocrit—along with any or all of the biological affects [sic] previously attributed to natural EPO." Appellee's Br. 21 (quoting *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 234). Amgen points out that although the passage at column 33, lines 11-22 does not actually use the term "therapeutically effective," other passages do, in fact, use the term. For example, at column 33, lines 43-50, Amgen notes, the patent actually uses the words "therapeutically effective" before explaining the required dosages for patients. According to Amgen, this indicates that "therapeutically effective" amounts are those related to healing or curing

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[6] The district court's claim construction references passages of the '933 patent found at column 33, lines 24-28 and column 33, lines 31-36. *Id.* at 214, 236, 245. The '422 patent contains identical passages at column 33, lines 16-20 and column 33, lines 23-28 respectively. These passages are part of a larger portion of the specification that runs from column 33, lines 11-28.

disease. Amgen also directs our attention to the portion of the specification found at column 33, lines 22-28. This passage states, "Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions . . . and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like." According to Amgen, only amounts of EPO producing effects—particularly increased hematocrit—that counteract these anemia-like diseases are "therapeutically effective." Amgen buttresses this argument with citations to the prosecution history where the patentee recounts the benefits of the claimed invention over prior art in treating disease.

The district court's claim construction is a matter of law, which we review de novo. *Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). In *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), we stated that claim construction must begin with the words of the claims themselves. *Id.* at 1312. A claim term has "the meaning that the term would have to a person of ordinary skill in the art. . . ." *Id.* at 1313. This meaning is ascertained "in the context of the entire patent, including the specification." *Id.* In particular, we stated in *Phillips* that "we must look at the ordinary meaning in the context of the written description and the prosecution history." *Id.* (quoting *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005)). When dealing with technical terms, we noted, a court should look to "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

Using *Phillips* as a guide, we turn first to the language of the claims. Neither the language of claim 1, nor the language of claim 2, of the '422 patent offer any guidance as to the meaning of "therapeutically effective."[7] However, several passages of the specification shed light on the meaning of the term. In particular, the text found at column 33, lines 11-22 states:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin *therapy procedures* practiced on mammals, including humans, to develop *any or all* of the *effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects* (such as plasma iron turnover effects and marrow transit time effects), *erythrocyte mass changes, stimulation of hemoglobin C synthesis* (see, Eschbach, et al., supra) *and, as indicated in Example 10, increasing hematocrit levels in mammals.*

'422 patent, col. 33, ll. 11-22 (emphases added). This language indicates that the claimed invention is used in "therapy" to produce "any or all" of the following "effects": stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin, and increasing hematocrit levels. Thus, increasing hematocrit is only one of the biological effects produced by the claimed invention. Accordingly, we agree with HMR/TKT that the district court misinterpreted this passage when it read it as limiting the claimed invention to

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[7] Claim 2 is an independent claim, which provides: "A pharmaceutically-acceptable preparation containing a therapeutically effective amount of erythropoietin wherein human serum albumin is mixed with said erythropoietin." '422 patent, col. 38, ll. 42-44.

products with "any or all" of the first four listed effects ascribed in vivo to EPO *and also* an increase in hematocrit.

Further, in the August 2, 1993 office action response, the patentee cited the above language of the specification and then stated, "It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be *therapeutically effective.*" (emphasis added). Thus, the patentee interpreted the passage at column 33, lines 11-22 of the specification as listing the therapeutic effects of the invention disclosed in the '422 patent. We think the district court made an artificial distinction between the first four effects listed in column 33, lines 11-22, stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, and stimulation of hemoglobin, and the fifth effect, an increase in hematocrit. The specification lists all five effects after stating that "any or all" of them may be an effect of therapy with the claimed invention. Thus, this section of the specification supports the construction that the '422 patent encompasses a pharmaceutical composition which produces "any or all" of the five listed effects.

As seen, the district court also determined that the specification indicates that the invention is limited to products that are "therapeutically effective" with respect to patients with anemia-like disorders, such as those listed at column 33, lines 22-28 of the '422 patent. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 235-36, 245-46. For this determination, the court relied on a passage that recites several diseases that may be treated by the claimed invention. The passage begins, "Included within the class of humans treatable with products of the invention . . . ." '422 patent, col. 33, ll. 22-28. However, this passage does not state that the claims encompass *only* products that treat such patients. Rather, by using the non-limiting word "included," it

suggests some persons, but not all persons, who may benefit from the invention.

Moreover, an additional section of the specification states, "It is noteworthy that the absence of in vivo activity for any one or more of the 'EPO products' of the invention is not wholly preclusive of therapeutic utility (see Weiland, et al., supra). . . ." *Id.* col. 36, ll. 9-12. We think the message of this passage is that "therapeutic utility" is not limited to products with "in vivo" effects. Thus, "therapeutic utility" is not dependent on the product having an effect in a living being, such as curing disease. Although this passage relates to a different EPO product than the one disclosed in claim 1 of the '422 patent, we think it illustrates the broad meaning of "therapeutic utility" used throughout the '422 patent. It shows that the patentee did not use the word "therapy" in order to limit the scope of the '422 patent to only EPO that cured disease. Thus, products that are not necessarily effective in actually curing disease in humans are encompassed by claim 1 of the '422 patent. Based on a reading of the claims in light of the specification, it appears that the patentee used the words "therapeutically effective" in order to broadly claim a pharmaceutical composition with a wide range of effects. Those effects do not *necessarily* include curing disease in humans.

During the prosecution of the '422 patent, in an office action response filed October 23, 1997, the patentee noted that recombinant EPO, like that found in the claimed invention, "is the first therapeutic product which can be used to effectively treat hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts." In our view, this statement merely lists some of the uses of the invention, without restricting the scope of the invention.

In sum, we disagree with the district court's claim construction to the extent that it limits the scope of claim 1 of the

'422 patent to EPO products that have one of the in vivo effects listed at column 33, lines 16-20 *and that also* increase hematocrit. We also disagree with the district court's conclusion that claim 1 of the '422 patent is limited to EPO products that may be used to treat patients with the disorders listed at column 33, lines 22-28 of the '422 patent's specification. On remand, the district court should utilize the following revised construction of "therapeutically effective:"

> A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals.

B.

Anticipation—The Goldwasser Reference

Based on its claim construction, the district court found in *Amgen III Validity & Literal Infringement Judgment* that the Goldwasser reference did not anticipate claim 1 of the '422 patent because Dr. Goldwasser's study was not effective in healing or curing. 339 F. Supp. 2d at 327. The parties dispute whether the Goldwasser reference anticipates claim 1 of the '422 patent under a revised claim construction. The purpose of the Goldwasser study was to examine EPO and its effects on erythropoiesis. Dr. Goldwasser acknowledged that mass production of EPO from recombinant DNA was not yet possible. Therefore, Dr. Goldwasser utilized EPO isolated from urine in an attempt to discover the chemistry and mode of action of EPO. In one portion of his study, Dr. Goldwasser performed a "very small clinical trial" using pure urinary

EPO ("uEPO"). The uEPO was administered to three anemic patients. Two patients received injections of 520 units twice daily for ten days. The third patient received a 1000 unit injection every 2-3 days for three weeks. In his 1984 grant application, Dr. Goldwasser described the results of the clinical study as follows:

> There was no significant change in hematocrit in any patient; each patient, however[,] showed an increase in reticulocyte count, with peaks at 9, 10[,] and 11 days. The first two patients had increased erythroid cells in the marrow and an increased plasma iron clearance rate. One of the first two patients showed an increase in red cell mass. These fragmentary data, need to be reinforced with more extensive and extended studies but they show that epo can have a physiological effect in this type of anemia.

In *Amgen I*, the district court noted that Dr. Goldwasser testified that this "abortive, three-patient trial was a failure." 126 F. Supp. 2d at 112.

The district court found that the Goldwasser reference did not anticipate claim 1 of the '422 patent because none of the effects listed in Dr. Goldwasser's study included healing or curing within the court's construction of "therapeutically effective." *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 327-34. HMR/TKT argues that under a revised construction of "therapeutically effective" that broadens the scope of claim 1 to encompass EPO that "elicits any of the biological effects listed in the specification [at column 33, lines 16-22]," Dr. Goldwasser's study anticipates. Amgen counters that even under a broader construction of "therapeutically effective," Dr. Goldwasser's study does not anticipate claim 1 of the '422 patent because its recombinant EPO ("rEPO") product differs in structure and function from the uEPO utilized in Dr. Goldwasser's study. Amgen argues that a remand is not necessary because

HMR/TKT admitted in its petition for a panel rehearing and rehearing en banc following *Amgen II* that the rEPO disclosed in claim 1 of the '422 patent differs in structure from naturally occurring uEPO.

Anticipation under 35 U.S.C. § 102 is a question of fact, which we review for clear error after a bench trial. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1369 (Fed. Cir. 2003); *Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1369 (Fed. Cir. 2004). The district court's factual findings on anticipation are clearly erroneous when "'although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" *Merck & Co*, 347 F.3d at 1369 (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)). A prior art reference anticipates a patent if it discloses all the limitations of the claimed invention. *Oney v. Ratliff*, 182 F.3d 893, 895 (Fed. Cir. 1999).

The district court's findings of fact on anticipation centered on whether the effects produced on patients in Dr. Goldwasser's study resulted in healing or curing. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 327. Under our construction of "therapeutically effective," however, the district court's findings of fact as to "healing or curing," while relevant, do not end the anticipation inquiry. Additional findings of fact are necessary to determine whether the Goldwasser study anticipates under our new construction of "therapeutically effective." When findings of fact are necessary under a revised claim construction, it is appropriate for us to remand to the district court. *See Seachange Int'l, Inc. v. C-Cor Inc.*, 413 F.3d 1361, 1381 (Fed. Cir. 2005) (remanding for the district court to consider anticipation after revising the claim construction). On remand, the district court should make findings of fact as to

whether the Goldwasser reference meets the "therapeutically effective" limitation under our construction.[8]

C.

Anticipation—The Sugimoto Patent

The Sugimoto patent, filed August 10, 1981, discloses a method for creating EPO-producing cells by creating hybrid cells from lymphoblastoids[9] and kidney tumor cells. The Sugimoto patent suggests using recombinant techniques to introduce the EPO genes from a human kidney tumor cell into human lymphoblastoids. Sugimoto patent, col. 1, l. 55–col. 2, l. 11. The patent involves in vivo production of EPO in which human lymphoblastoid cells capable of producing EPO are transferred to an animal body. The Sugimoto patent explains that the EPO produced by the animal according to this technique is then "collected easily by purification and separation techniques using conventional procedures . . . ." *Id.* col. 3, ll. 51-53.

In *Amgen I*, the district court found that the Sugimoto patent did not anticipate claim 1 of the '422 patent because it was not enabled. 126 F. Supp. 2d at 109. The court considered the testimony of Amgen's expert, Dr. Allan Erslev, who stated that the Sugimoto procedure was "very complex." *Id.* at 108. Dr. Erslev stated that no one had used the Sugimoto process prior to 1984, even though it would have been highly profitable if successful. *Id.* After recounting Dr. Erslev's testimony, the court discounted HMR/TKT's arguments. *Id.* HMR/TKT had put Dr. Michael

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[8] If, on remand, the district court finds that the Goldwasser reference contains the "therapeutically effective" limitation, it must then determine whether the uEPO meets the other limitations of claim 1 of the '422 patent.

[9] Lymphoblastoids are cells that are typically isolated from patients with leukemia, which is a cancer of the blood. *Amgen I*, 126 F. Supp. 2d at 106.

Heartlein on the stand. By attempting to replicate the Sugimoto process, Dr. Heartlein produced cells that generated six times as much EPO as their parent cells. *Id.* at 108-09. The court found that Dr. Heartlein's experiments were not sufficient to show enablement, however, because Dr. Heartlein followed a different procedure than the one disclosed in the Sugimoto patent. First, Dr. Heartlein used an in vitro technique rather than an in vivo technique like that disclosed in the Sugimoto patent. *Id.* at 109. Second, the district court found that Dr. Heartlein used different starting materials than the Sugimoto patent because he could not obtain kidney tumor cells like those disclosed in the Sugimoto patent. *Id.* Based on the foregoing, the district court found that HMR/TKT had failed to demonstrate that the Sugimoto patent was enabled by clear and convincing evidence. *Id.* at 108–09.

On appeal, we ruled in *Amgen II* that the district court had erred in placing the burden of proving enablement on HMR/TKT. *Id.* at 1357. We indicated that the Sugimoto patent should have been presumed enabled and that Amgen should have had the burden of proving otherwise. *Id.* at 1355.

On remand, the district court affirmed its previous holding of non-enablement, finding that "Amgen has shown by a preponderance of the evidence that Sugimoto is not enabled . . . ." *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 307. The court based its conclusion that the Sugimoto patent was not enabled on three findings. First, the court noted that the Sugimoto patent did not disclose the starting materials necessary to repeat the process it describes. *Id.* at 307-09. The Sugimoto patent required the use of kidney tumor cells, but the inventor neither deposited these cells publicly nor did he disclose them so that a person of ordinary skill in the art could procure them. *Id.* at 307. Second, the court found that the Sugimoto patent was not enabled because it did not teach a person of ordinary skill in

the art how to select EPO-producing hybrid cells. The court based its finding largely on the testimony of Dr. Howard Green, a cell biologist with over forty years of experience, who stated that although methods for selecting hybrids were available at the time the Sugimoto patent was filed, they were inconsistently successful and required undue experimentation to produce results. *Id.* at 309. Third, the court found that the Sugimoto patent did not enable a method for purifying EPO even though the Sugimoto patent claimed to teach how to produce purified EPO. *Id.* at 311-12. The court found support for this finding in the testimony of Dr. Green, *id.* at 311, as well as in evidence that the Sugimoto patent's disclosure still had not been put into practice years after it issued in March of 1983, *id.* at 312. In addition, in connection with all three findings, the court noted that Dr. Heartlein had failed to duplicate the Sugimoto starting materials, selection methods, or purification techniques when using the disclosure of the Sugimoto patent. *Id.* at 307-08, 311-12.

HMR/TKT makes several arguments for reversing the district court's finding of non-enablement. With regard to the district court's finding that the cells necessary for the Sugimoto procedure were not adequately disclosed or deposited, HMR/TKT urges that the description of the starting materials in the Sugimoto patent was sufficient despite the fact that the cells were not deposited. HMR/TKT notes that the Patent and Trademark Office found that there was an adequate written description and that a person of ordinary skill in the art would have understood the disclosure. HMR/TKT asserts that the district court's use of Dr. Heartlein's experiments as proof of non-enablement was flawed because the district court previously found in *Amgen I* that Dr. Heartlein did not follow the Sugimoto patent's disclosure.

Amgen defends the district court's decision on remand by arguing that the district court correctly identified deficiencies in the Sugimoto patent's disclosure. First, Amgen argues that

the lack of starting materials is illustrated by both Amgen's and Dr. Heartlein's inability to obtain the kidney tumor cells described in the Sugimoto patent. Amgen also notes that EPO-producing cells prior to Dr. Lin's invention were "poor producers." In addition, Amgen argues that the district court correctly found that the Sugimoto patent was not enabled based on the lack of disclosure of a method for hybrid cell selection or purification.

In order to anticipate, a prior art reference must not only disclose all of the limitations of the claimed invention, but also be enabled. *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). A reference is enabled when its disclosures are sufficient to allow one of skill in the art to make and use the claimed invention. *Id.* (quoting *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001)). Like a patent, a prior art reference is enabled even if some "routine experimentation is required in order to practice a claimed invention, but . . . such experimentation must not be 'undue.'" *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). When considering whether or not a prior art reference requires "undue experimentation" we look at the reference from the perspective of a person of ordinary skill in the art. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988).

We established in *Amgen II* that when a piece of prior art is a patent, like the Sugimoto patent, there is a presumption of enablement. 314 F.3d at 1355. The patentee, Amgen, must present persuasive evidence of non-enablement to overcome this presumption. *Id.* As seen, in *Amgen II*, we vacated and remanded the finding of non-enablement with regard to claim 1 of the '422 patent. On remand, the district court found that Amgen had met its burden of proving by a preponderance of the evidence that the Sugimoto patent was not enabled. 339 F. Supp. 2d at 306. We review the district court's ultimate determination of enablement de novo while the underlying

factual inquiries made by the district court are reviewed for clear error. *Enzo Biochem*, 188 F.3d at 1369.

The district court's factual finding that the Sugimoto patent did not adequately disclose the starting materials was not clearly erroneous. The court based its conclusion on the testimony of several scientists with experience in the field of erythropoeisis, including Dr. Green, Dr. Lin, and Dr. Harvey Lodish, a research biologist at the Whitehead Institute and the Massachusetts Institute of Technology. Dr. Green testified that Dr. Heartlein, who attempted to duplicate the Sugimoto disclosure, searched "for a long time and in many different ways" to find a suitable cell line and finally settled on a liver tumor cell line—not a kidney tumor cell line like Sugimoto's. Dr. Lin testified that he had searched extensively for an EPO-producing cell line during his research, but never acquired a EPO-producing kidney tumor cell line. Dr. Lodish stated that the Sugimoto patent failed to demonstrate that the kidney tumor cells disclosed in the patent actually produced EPO. In addition, Amgen presented evidence that it failed to locate any kidney tumor cells, like those described in the Sugimoto patent, despite repeated efforts to do so. At the same time, we do not see clear error in the court's finding that Dr. Heartlein's non-conforming experiments show that a person of ordinary skill in the art would not be able to obtain the required kidney tumor cells based on the Sugimoto patent's disclosures. The failure of Dr. Heartlein to obtain the cells disclosed by the Sugimoto patent and the expert testimony of Drs. Green, Lin, and Lodish support this finding. Further, Sugimoto did not deposit the EPO-producing kidney tumor cells described in the Sugimoto patent. In sum, the Sugimoto patent was not enabled due to the patentee's failure to adequately describe how to derive the starting materials or deposit the cells. *See In re Wands*, 858 F.2d at 735 ("Where an invention depends on the use of living materials such as microorganisms or cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these

living materials) solely by means of a written disclosure."). Because we discern no clear error in the district court's finding that the Sugimoto patent's failure to disclose or deposit the starting materials necessary to produce EPO rendered the patent not enabled, it is unnecessary for us to address Amgen's arguments that the Sugimoto patent also did not teach how to select hybrid cells and that the Sugimoto patent did not disclose a means for purifying EPO.

D.

Obviousness—The Sugimoto Patent

The district court held in *Amgen I* that the Sugimoto patent did not render claim 1 of the '422 patent obvious because the Sugimoto patent was not enabled. 126 F. Supp. 2d at 114 & n.29. In *Amgen II* we vacated this finding and remanded because non-enablement does not preclude a finding of obviousness. 314 F.3d at 1357. On remand, in *Amgen III Validity & Literal Infringement Judgment*, the district court again concluded that the Sugimoto patent did not render claim 1 of the '422 patent obvious. In reaching this conclusion, the court considered the scope and content of the prior art, differences between the claimed invention and the prior art, the level of ordinary skill in the art, and reasonable expectation of success. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 316-19. The court also placed emphasis on the "objective indicia of non-obviousness," or "secondary considerations." *Id.* at 314, 319. Specifically, the court found that there had been a long-felt, but unmet need for EPO-producing cells prior to Dr. Lin's discovery. *Id.* at 319. Thus, the district court concluded that HMR/TKT "failed to persuade the Court by clear and convincing evidence that the asserted claims of [Amgen's patents] were obvious in light of Sugimoto." *Id.* at 325. HMR/TKT appeals the district court's ruling.

We have considered the various arguments made by HMR/TKT on the obviousness issue. Having done so, we see no reason to disturb the ruling of the district court that HMR/TKT failed to establish that claim 1 of the '422 patent was obvious in view of the Sugimoto patent.

II.

The '080 Patent

As seen, in *Amgen III Doctrine of Equivalents Judgment*, the district court ruled that claims 2-4 of the '080 patent were not invalid and that Amgen was not estopped from asserting infringement under the doctrine of equivalents. 287 F. Supp. 2d at 160. Accordingly, the court reinstated its vacated finding in *Amgen I* that claims 2-4 of the '080 patent were infringed under the doctrine of equivalents by HMR/TKT's HMR4396 product. *Id.* The only issue before us on appeal is infringement under the doctrine of equivalents. Claims 2-4 provide:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.
>
> 3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount [of] an erythropoietin glycoprotein product according to claim 1, 2 or 3.

'080 patent, col. 38, ll. 39-53. Claims 2-4 of the '080 patent each contain the limitation that the "erythropoietin glyco-

protein comprises the mature erythropoietin amino acid sequence of FIG. 6." The sequence shown in Figure 6 of the '080 patent has a DNA sequence coding for 166 amino acids. However, as noted above, mature human EPO actually contains 165 amino acids, because the 166th amino acid, arginine, is cleaved off prior to the EPO's secretion from the cell. The question before us is whether prosecution history estoppel bars Amgen from claiming that claims 2-4 of the '080 patent encompass EPO with 165 amino acids under the doctrine of equivalents. This is critical because HMR/TKT's EPO product, HMR4396, has only 165 amino acids. *Id.* at 129.

A.

The application that resulted in the '080 patent was filed on June 6, 1995 as Application No. 08/468,556 ("the '556 application"). The '556 application, which contained 60 claims, was a continuation-in-part of the '024 application. In the first preliminary amendment of the '556 application, the patentee cancelled claims 1-60 and added claims 61-67. Of the seven new claims added by amendment, claims 61-64 comprised the only independent product claims. Proposed claims 61-64 provided as follows:

> 61. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having glycosylation which differs from that of human urinary erythropoietin.
>
> 62. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE.
>
> 63. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources and free of other human proteins.

64. The in vivo biologically active erythropoietin product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complimentary strands; and

(b) isolating said erythropoietin product therefrom.

The patentee made a second preliminary amendment to the '556 application on December 20, 1995. In the second preliminary amendment, claims 61-63 were cancelled, claim 64 was amended, and a new claim, claim 68, was added. The amended version of claim 64 provided as follows:

64. The non-naturally occurring in vivo biologically active erythropoietin product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complimentary strands; and

(b) isolating said erythropoietin product therefrom.

Claim 68, which was added in the second preliminary amendment, provided as follows:

68. A non-naturally occurring erythropoietin product of the process comprising the steps of:

a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof; and

b) isolating an erythropoietin product therefrom.

In the third and final amendment made to the '556 application for the '080 patent, the patentee cancelled claims 64 through 68 and added claims 69-75. Claims 70-72, which issued as claims 2-4 of the '080 patent, provided as follows:

70. An isolated erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and is not isolated from human urine.

71. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6.

72. A pharmaceutical composition comprising a therapeutically effective amount [of] an erythropoietin glycoprotein product according to claim 69, 70 or 71.

As seen, after the first preliminary amendment, the claims of the '556 application broadly encompassed an isolated human EPO product. The application claimed an EPO product made using the human EPO DNA sequence set out in Figure 6 or the monkey EPO DNA sequence set out in Figure 5. With the second preliminary amendment, the patentee added claim 68, which claimed an EPO product made using the amino acid sequence for EPO set out in Figure 6 "or a

fragment thereof." With the third preliminary amendment, the patentee removed all references to non-human monkey EPO and also deleted claims for an EPO product made using "a fragment" of the amino acid sequence of Figure 6. Instead, as of the third preliminary amendment, the '556 application claimed only a human EPO product having the complete amino acid sequence of Figure 6.

B.

In *Amgen I*, the district court found that the amendments to the '556 application were made to preempt a double-patenting rejection based on claim 1 of the '933 patent.[10] 126 F. Supp. 2d at 135. The district court held that an amendment made to avoid a double-patenting rejection is not an amendment related to patentability. *Id.* at 136. Therefore, the court held that Amgen was not estopped from claiming that EPO with a 165-amino acid sequence infringed the asserted claims of the '080 patent under the doctrine of equivalents. *Id.*

In *Amgen II*, citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740-41 (2002) ("*Festo II*"), we vacated the district court's finding and held instead that Amgen's double-patenting amendment was an amendment related to patentability that gave rise to prosecution history estoppel. 314 F.3d at 1345. We vacated the district court's finding of infringement of the '080 patent under the doctrine of equivalents and remanded for "an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel." *Id.* These "narrow ways" were first set forth in

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[10] Claim 1 of the '933 patent provides:

> A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

'933 patent, col. 38, ll. 18-22.

Festo II. They are (i) showing that an equivalent was unforeseeable; (ii) demonstrating that the purpose for an amendment was merely tangential to the alleged equivalent; or (iii) establishing "some other reason" that the patentee could not have reasonably been expected to have described the alleged equivalent. 535 U.S. at 740-41.

On remand, in *Amgen III Doctrine of Equivalents Judgment*, the district court evaluated whether any one of the three grounds for rebutting the *Festo* presumption of estoppel had been demonstrated by Amgen. 287 F. Supp. 2d at 147-59. The court determined that Amgen had failed to show that a 165-amino acid EPO was unforeseeable at the time of the third preliminary amendment. *Id.* at 149. However, the court determined that Amgen had succeeded in showing that the third preliminary amendment, which restricted the literal scope of the '080 patent to EPO having the complete amino acid sequence shown in Figure 6, was added only to limit the '080 patent to human EPO products. *Id.* at 152. The court found that the third preliminary amendment was therefore no more than tangentially related to the 165-amino acid equivalent. *Id.* at 154. The court based this finding on the prosecution history, noting that "the chronology and language of the amendments support Amgen's position that it added the amendment in question (the third amendment) to distinguish the '080 patent from the '933 patent on the basis that the '080 was limited to *human* EPO." *Id.* at 152 (emphasis in original). The human EPO limitation thus was merely tangential, the district court found, to the 165-amino acid equivalent. The court buttressed its finding of tangentiality with a "reasonable inference" that the amendment was not made with the intention of surrendering equivalents because, as of December of 1996, when the third preliminary amendment was made, the Patent and Trademark Office and Amgen both were aware that mature EPO had 165 amino acids. *Id.* at 153.

Although the district court found that the *Festo* presumption was rebutted because the amendment limiting the claims of the '080 patent to EPO with the amino acid sequence of Figure 6 was tangential to EPO having a 165-amino acid sequence, it set forth an alternate rationale based on the "some other reason" language in *Festo II*. The court looked to both extrinsic and intrinsic evidence suggesting that the drafter of the amendment, as well as those of ordinary skill in the art, would have considered the amendment to cover all human EPO, regardless of whether or not the EPO had 165 or 166 amino acids. *Id.* at 157. In essence, the court construed the claims based on the extrinsic record (with support from the intrinsic record). *Id.* The court reasoned that this evidence reflected a "shortcoming[ ] of language" or "linguistic" limitation, which were mentioned in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1372 (Fed. Cir. 2003) (en banc) ("*Festo III*"), as possible reasons for rebuttal of the Festo presumption. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 159. The court then found that those equivalents encompassed by this construction were not surrendered, relying on the "some other reason" exception to the *Festo* presumption of surrender of equivalents. *Id.*

HMR/TKT argues on appeal that the district court erred in finding that Amgen's third preliminary amendment was merely tangential to the equivalent EPO having a 165-amino acid sequence. It contends that if the patentee had intended solely to limit the scope of claims 2-4 of the '080 patent to *human* EPO, the patentee would have used the word "human" to describe the EPO. Instead, according to HMR/TKT, the third preliminary amendment uses the word "mature," while both of the previous amendments used the word "human" to describe the EPO claimed. HMR/TKT urges that the district court also erred by finding that Amgen rebutted the *Festo* presumption based on "some other reason." HMR/TKT argues that Amgen amended the claims of the '080 patent to

include only a 166-amino acid EPO out of fear of a new matter rejection, which does not fall under *Festo*'s "some other reason" criterion.

Amgen counters that the district court was correct in its conclusion because the purpose of the third preliminary amendment was to distinguish the '080 patent, which encompasses only *human* EPO, from claim 1 of the '933 patent, which encompasses both human and animal EPO. In support of its argument, Amgen recites its remarks during prosecution "that claims 69, 70, and 71 [currently claims 2-4 of the '080 patent] all differ in scope from glycoprotein claim 1 of U.S. 5,547,933 in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6. Claim 69 [currently claim 1 of the '080 patent] (like ['933] glycoprotein claim 1) recites carbohydrate differences in comparison to human urinary [EPO] and claim 70 [currently claim 2 of the '080 patent] recites a negative limitation with respect to isolation from human urine." (footnote omitted). Based on the foregoing statement in the patentee's remarks accompanying the third preliminary amendment, Amgen contends that the amendment was meant to distinguish Amgen's EPO from naturally-occurring EPO through differences in glycosylation, or "carbohydrate differences." Thus, Amgen argues that the mention of the EPO sequence of Figure 6 was merely tangential. Further, Amgen defends the district court's conclusion that Amgen successfully rebutted the *Festo* presumption under the "some other reason" rationale. Amgen argues that because a person of ordinary skill in the art would have understood the claims to encompass a 165-amino acid equivalent, the *Festo* presumption was rebutted. Finally, Amgen argues that the district court erred in finding that a 165-amino acid equivalent was foreseeable because the patentee expected the claims to encompass this equivalent.

C.

The burden of rebutting the *Festo* presumption lies with the patentee. *Festo III*, 344 F.3d at 1368. Whether a patent-holder has successfully rebutted the *Festo* presumption of the surrender of equivalents is a question of law, which we review de novo. *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1376 (Fed. Cir. 2005); *see also Festo III*, 344 F.3d at 1368; *Biagro W. Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296, 1302 (Fed. Cir. 2005); *Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1351 (Fed. Cir. 2004). For the reasons which follow, we uphold the district court's finding that Amgen failed to show that EPO with a 165-amino acid sequence was not foreseeable at the time of the amendment. However, we hold that the district court erred when it held that Amgen had met its burden of rebutting the *Festo* presumption under both the tangentiality and "some other reason" rationales.

The presumption that equivalents are surrendered may be rebutted if a patentee shows that "one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo III*, 344 F.3d 1365 (quoting *Festo II*, 535 U.S. at 741). As noted, in *Festo II*, the Supreme Court listed three ways in which a patentee may make this showing. First, the patentee may demonstrate that "the equivalent [would] have been unforeseeable at the time of the [amendment]." 535 U.S. at 740-41. Second, the patentee may show that "the rationale underlying the amendment [bears] no more than a tangential relation to the equivalent in question." *Id.* Third, a patentee may demonstrate that "there [is] some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." *Id.*

In *Festo III*, we offered some guidance as to what must be shown by a patentee in order to succeed in rebutting the *Festo* presumption under each of the three showings enumerated by the Supreme Court. In order to demonstrate that an invention

is not foreseeable, a patentee may utilize extrinsic evidence. 344 F.3d at 1369. We suggested that after-arising technology is more likely to be unforeseeable than old technology, but did not set forth any hard or fast rule on foreseeability. *Id.* We stated that "if the alleged equivalent were known in the prior art in the field of the invention, it certainly should have been foreseeable at the time of the amendment." *Id.* With regard to the tangentiality of an amendment to an equivalent, we did not set forth any concrete definition, but we did note that an amendment "made to avoid prior art that contains the equivalent in question is not tangential; it is central to allowance of the claim." *Id.* Thus, an amendment is tangential when the "reason for [it] was peripheral, or not directly relevant, to the alleged equivalent." *Id.* The determination of whether or not an amendment is merely tangential to the equivalent is based on the "patentee's objectively apparent reason for the narrowing amendment." *Id.* Thus, the inquiry must be based on the intrinsic record alone and, if necessary, expert testimony to aid in interpretation of that record. *Id.* Finally, we noted that the third way to rebut the *Festo* presumption, the "some other reason" route, is a narrow one. *Id.* at 1370. We stated that "the third criterion may be satisfied when there was some reason, such as the shortcomings of language, why the patentee was prevented from describing the alleged equivalent when it narrowed the claim." *Id.*

1.

With regard to the first *Festo* rebuttal argument, foreseeability, we see no error in the district court's holding that, at the time the third preliminary amendment was made, EPO with 165 amino acids was a foreseeable equivalent. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 147-49. We reject Amgen's assertion that the relevant inquiry is whether it was "objectively foreseeable that the amended claim language would not read on the accused equivalent." Appellee's Br. at 74. The question of how a person of

ordinary skill in the art would understand claims 2-4 of the '080 patent is one of claim construction, which was settled in *Amgen II*. 314 F.3d at 1344-45 (affirming the district court's construction of claims 2-4 as being limited to EPO with 166 amino acids). EPO with a 165-amino acid sequence was a foreseeable equivalent because the patentee admittedly knew about the 165-amino acid equivalent at the time of the third preliminary amendment. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 157 (finding that during prosecution Amgen informed the examiner that human EPO has 165 amino acids); *see Festo III*, 344 F.3d at 1369 (noting that if an equivalent is known in the field, then it is foreseeable); *Glaxo Wellcome, Inc.*, 356 F.3d at 1355-56 (finding that a patentee did not rebut the presumption of surrender when a person of ordinary skill in the art at the time of the amendment would have considered the equivalent).

2.

We next examine whether Amgen has met its burden of showing that the reason for the addition of the reference to the "amino acid sequence of FIG. 6" was merely tangential to the alleged equivalent.

In *Insituform Technologies, Inc. v. CAT Contracting, Inc.*, 385 F.3d 1360 (Fed. Cir. 2004), we were asked to review whether a patentee had successfully rebutted the surrender of equivalents. *Id.* at 1370-71. The patented method in *Insituform* involved using a vacuum to impregnate a flexible tube with resin. *Id.* at 1362-63. During prosecution, the patentee limited the number of suction cups that could be placed on the tube to create the vacuum to just one cup. *Id.* at 1366. The amendment that limited the number of vacuum cups was made to overcome prior art which had a single vacuum source located at the end of the tube a distance from the resin source. *Id.* at 1370. The reason for the amendment was to clarify the location of the vacuum source relative to the resin—not to limit the number of vacuum cups. *Id.* Thus, we ruled that the

reason for the amendment was merely tangential to the alleged equivalent using multiple cups. *Id.* Accordingly, we held that the patentee in *Insituform* successfully rebutted the *Festo* presumption of surrender of the equivalent in question.

Amgen was required to show that the reason for adding the requirement in the third preliminary amendment that EPO have 166 amino acids was peripheral to the 165-amino acid equivalent. *See Festo III*, 344 F.3d at 1369. As seen, the third preliminary amendment was made to avoid a double patenting rejection in light of the '933 patent. *Amgen I*, 126 F. Supp. 2d at 135. Thus, the 165-amino acid equivalent is only tangential if the patentee's reason for limiting the '080 patent to EPO with 166 amino acids was unrelated to distinguishing the scope of the '080 patent from the scope of the '933 patent.

We must reject Amgen's argument that the sole reason for the amendment requiring EPO with 166 amino acids was to limit the '080 patent to *human* EPO and that therefore the amendment was merely tangential to a 165-amino acid equivalent. As seen, in claim 1 the '933 patent claimed:

> A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

'933 patent, col. 38, ll. 18-22. Thus, claim 1 contains no limitation pertaining to human or non-human EPO. Claim 1 of the '933 patent, which covers both human and non-human EPO, also lacks any limitation concerning the amino acid sequence of the claimed EPO product. Accordingly, claim 1 of the '933 patent broadly encompasses EPO with any amino acid sequence, which would include amino acid sequences differing from that set forth in Figure 6.

We think Amgen's third preliminary amendment did more than limit the scope of the asserted claims of the '080 patent

to human EPO. The third preliminary amendment limited the '556 application, and consequently the '080 patent, to EPO having 166 amino acids. Claim 68, which was added with the second preliminary amendment to the '556 application, encompassed cells "encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof." Thus, after the second preliminary amendment, the '556 application and the '933 patent overlapped in claim scope. That is because the '556 application encompassed EPO having the incomplete amino acid sequence set forth in Figure 6. Likewise, claim 1 of the '933 patent encompassed EPO having any amino acid sequence, which would include an incomplete amino acid sequence of Figure 6. In other words, an incomplete amino acid sequence of Figure 6 (a "fragment") was encompassed by both the '556 application and the '933 patent. The deletion of "or fragment thereof" with the third preliminary amendment limited the '556 application to the complete 166-amino acid sequence shown in Figure 6. This limitation reduced the overlap between the scope of the '556 application, which encompassed only EPO with the complete amino acid sequence of Figure 6, from the scope of claim 1 of the '933 patent, which encompassed EPO with any amino acid sequence. Indeed, as the inventor himself stated in the remarks accompanying the third preliminary amendment, the amended claims "all differ in scope from glycoprotein claim 1 of [the '933 patent] in specifying that the claimed subject matter comprises the mature human erythropoietin *sequence of Figure 6*." Third Preliminary Amendment at 164 (Dec. 20, 1996), *quoted in Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 152 n.36 (emphasis added) (footnote omitted). Accordingly, the limitation added in the third preliminary amendment may have been central to overcoming a double patenting rejection in light of claim 1 of the '933 patent. Under these circumstances we cannot say that the reason for the addition of the limitation pertaining to the complete amino acid sequence of Figure 6 was merely tan-

gential to the alleged 165-amino acid equivalent. Thus, unlike *Insituform*, where it was clear that the amendment in question was not made to limit the number of cups and overcome the prior art, the requirement that EPO have exactly 166 amino acids may have been central to the allowance of claims 2-4 over a double patenting rejection.

Finally, we think that if the patentee had wished only to limit the claims to human EPO, the patentee could have done so by continuing to use the adjective "human" when referring to EPO in the third preliminary amendment; instead the patentee chose to further narrow the claims in the third preliminary amendment by making reference to the specific sequence in Figure 6 rather than human EPO. We thus hold that Amgen has not met its burden of showing that the addition of the "the mature amino acid sequence of FIG. 6" amendment was tangential to a 165-amino acid equivalent.

3.

In the alternative, the district court relied on the "some other reason" language in the Supreme Court's *Festo II* decision in ruling that Amgen had rebutted the *Festo* presumption of surrender of equivalents. In *Festo II*, the Court held that the presumption of the surrender of equivalents could be rebutted by showing that "there [is] some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." 535 U.S. at 740-41. As previously noted, the district court based its conclusion that Amgen had rebutted the *Festo* presumption under the "some other reason" rationale on its finding that, before the patentee made the third preliminary amendment, the patentee disclosed information to the Patent and Trademark Office concerning the fact that human EPO has 165 amino acids. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 157. The district court also relied on extrinsic evidence that a person of ordinary skill in the art would understand that Amgen meant to claim human EPO

having either 165 or 166 amino acids at the time the third preliminary amendment was made. *Id.* The court reasoned that Amgen had rebutted the *Festo* presumption under the "some other reason" criterion because the patentee could not have reasonably been expected to have described the 165-amino acid equivalent because those of skill in the art would have interpreted the amendment to cover the 165-amino acid equivalent. *Id.* at 158.

However, the district court's analysis does not correctly apply the Supreme Court's explanation of the "some other reason" rebuttal argument: the other reason must be such that the patentee could "not reasonably be expected" to write a claim to encompass the equivalent, *see Festo II*, 535 U.S. at 741, such as a shortcoming of language, *Festo III*, 344 F.3d at 1370. The patentee knew of the 165-amino acid sequence at the time of the amendment, *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 157, but chose to limit the claims to the 166-amino acid sequence depicted in Figure 6. Contrary to Amgen's argument, whether the patentee, the examiner, or a person of skill in the art may have thought the claims encompassed EPO with 165 amino acids does not excuse the patentee's failure to claim the equivalent. *See Biagro*, 423 F.3d at 1307 (rejecting the patentee's argument that the "some other reason" rebuttal argument applied when the patentee allegedly understood the claim language to refer to the equivalent in question). Further, there were no shortcomings of language that might have prevented the patentee from claiming EPO having 165 amino acids. The patentee could have simply claimed mature human EPO without reference to Figure 6. Alternatively, the patentee could have claimed, as it did prior to the third preliminary amendment, EPO having the amino acid sequence disclosed in Figure 6 or a "fragment thereof." In short, there was no linguistic barrier to claiming EPO comprised of 165 amino acids. Amgen has not argued on appeal, nor do we find, that any other reason exists that might rebut the *Festo* presumption. Therefore, we

find that the patentee could have reasonably been expected to accurately point out and particularly claim the 165-amino acid sequence.

The facts in this case are analogous to those in *Festo III*, where we ruled that the *Festo* presumption was not rebutted by "some other reason." In *Festo III*, we rejected Festo's argument that it was not estopped from asserting the doctrine of equivalents because the patentee "could not reasonably have been expected to have drafted a claim to cover what was thought to be an inferior and unacceptable design." 344 F.3d at 1372-73. Like the patentee in *Festo*, who knew about the "inferior" equivalent, the patentee of the '080 patent knew about the 165-amino acid sequence at the time of the amendment, but still chose to claim the incorrect 166-amino acid sequence in Figure 6. We conclude that Amgen has not rebutted the *Festo* presumption based on "some other reason."

In sum, we uphold the district court's finding that the 165-amino acid EPO equivalent was foreseeable at the time of the third preliminary amendment. The district court erred, however, in finding that Amgen successfully rebutted the *Festo* presumption of surrender of equivalents under both the tangentially related rebuttal argument and the "some other reason" rebuttal argument. This means that HMR/TKT cannot be found to have infringed the claims 2-4 of the '080 patent under the doctrine of equivalents. Accordingly, the judgment of infringement of claims 2-4 is reversed. It is unnecessary for us to reach HMR/TKT's alternative argument by way of affirmative defense that claims 2-4 of the '080 patent are invalid as anticipated by the Goldwasser reference.

III.

The '698 and '349 patents

The '698 patent is directed to a process for producing EPO in host cells using recombinant DNA techniques. On remand, in *Amgen III Validity & Literal Infringement Judgment*, the

district court rejected HMR/TKT's argument that the asserted claims of the '698 patent (claims 4-9) are invalid because they lack an adequate written description. The court also rejected HMR/TKT's argument that the asserted claims were not enabled. Having rejected HMR/TKT's validity challenges, the court found claims 4-9 of the '698 patent literally infringed.

The '349 patent is directed to vertebrate cells capable of producing EPO and a process for making EPO using the claimed cells. On remand, the district court rejected HMR/TKT's argument that the asserted claims of the '349 patent (claims 1, 3, 4, 6, and 7) were invalid by reason of obviousness. Since the district court already had ruled in *Amgen I* that claims 1, 3, 4, and 6 of the '349 patent were infringed, in *Amgen III Validity & Literal Infringement Judgment* it only was necessary for the court to address Amgen's claim that HMR/TKT's HMR4396 literally infringed claim 7 of the '349 patent. Doing so, the court found literal infringement. 339 F. Supp. 2d at 258, 336.

On appeal, HMR/TKT argues that the district court made various claim construction errors and also erred in its validity and infringement rulings in the case of both the '698 and '349 patents. We have carefully considered all of HMR/TKT's arguments relating to the '698 and '349 patents. Having done so, we see no error in the district court's legal conclusions; nor do we see clear error in its findings of fact. Accordingly, we affirm in all respects the court's rulings with respect to the '698 and '349 patents.

CONCLUSION

For the foregoing reasons, we vacate the district court's judgment that claim 1 of the '422 patent is not invalid under 35 U.S.C. § 102(a) and remand to the district court for a determination of whether, in view of our construction of the limitation "therapeutically effective," claim 1 is anticipated

by the Goldwasser reference and for such further proceedings as may be necessary.[11] We reverse the court's judgment that HMR/TKT infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We affirm the court's judgment that HMR/TKT infringes claims 4-9 of the '698 patent and claims 1, 3, 4, 6, and 7 of the '349 patent.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART, and REMANDED

[11] See footnote 10, *supra*.

MICHEL, *Chief Judge*, dissenting-in-part.

I write separately to voice my strong disagreement with the majority's holdings that (1) contrary to the district court's construction, "therapeutically effective" in claim 1 of the '422 patent means simply eliciting in vivo biological effects even if not tending to cure certain diseases and (2) claim 1 of the '422 patent could therefore be invalid in light of the Goldwasser reference, which describes a prior art compound eliciting biological activity without curing. Because the majority concludes that the district court erred in construing "therapeutically effective" to mean having a disease-curing effect, it remands the case for a re-adjudication of whether the Goldwasser reference anticipates claim 1 of this particular patent, only one of several asserted.

At the outset, I compliment the district court for the meticulous attention it has given to this extraordinarily complicated, highly-technical, and very difficult case. The district court's two opinions on remand, the subject of our present review, were well-reasoned, well-grounded in the evidence, and well-written. The trial court clearly exerted tremendous effort to carefully consider all the issues raised by the parties as well as our remand instructions in *Amgen II*.

After discovery, the district court conducted a three-day Markman hearing and a bench trial spanning twenty-three days in 2000 and then, following our remand, a second *Markman* hearing and second bench trial spanning nine days in 2003. The district court also took the creative steps of employing Professor Chris Kaiser of the Massachusetts Institute of Technology as a technical advisor on the underlying technology and Michele D. Beardslee as a special master to aid in researching the law, analyzing the issues, and drafting the remand opinion. Assisted by them, the district court spent more than ten months rendering its revised claim constructions and making extensive findings of fact and conclusions of law; it subsequently issued two opinions, together totaling

over 360 pages. Plainly, these decisions were not reached in a haphazard or hurried manner by a court intimidated by either the science or the law. On the contrary, the district court's management and resolution of this case is, I think, a model for all trial courts confronted with such patent suits.

I.

The district court construed "therapeutically effective amount" to mean "a quantity that produces a result that in and of itself helps to heal or cure." *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 245. It further elaborated that a therapeutically effective amount would elicit certain in vivo biological effects, such as those described in the specification, col. 33, ll. 17-22, (i.e., stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin C synthesis, and increasing hematocrit levels), which reflect a "healing" or "curing" effect in "patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiological anemias, and the like." '422 patent, col. 33, ll. 23-28. I believe the court correctly recognized that merely eliciting a biological effect is not the same as being therapeutically effective.

Indeed, prior art compounds could trigger the very in vivo biological effects enumerated in the specification but were utterly incapable of "healing" or "curing" the class of patients described in the '422 patent. Notably, an article published in the Renal Extrarenal Sources of Erythropoietin Journal in 1971 revealed that a patient suffering from renal anemia was treated with an urinary EPO preparation but, despite experiencing an increase in reticulocytes, died five days later. The district court was particularly aware of this article and even mentioned it when addressing the issue of obviousness after

the first bench trial. *See Amgen I*, 126 F. Supp. 2d at 116. Had this uEPO or any other prior art EPO product been shown to "heal" or "cure" anemia or similar blood disorders, there would have been little need for the claimed invention.

When a compound is truly "therapeutically effective," that is, when it "heals" or "cures" such a blood disorder, it necessarily increases hematocrit as well as causes one or more of the other listed in vivo biological effects. Reading lines 17-22 of column 33 in context, the patentee clearly recognized this.

> As previously indicated, recombinant-produced and synthetic products of the invention share, to varying degrees, the in vitro biological activity of EPO isolates from natural sources and consequently are projected to have utility as substitutes for EPO isolates in culture media employed for growth of erythropoietin cells in culture. Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., . . . *and*, as indicated in Example 10, *increasing hematocrit levels* in mammals.

'422 patent, col. 33, ll. 6-22 (emphasis added). This disclosure clarifies three aspects of the claimed invention. First, the claimed EPO shares the in vitro biological activity of natural EPO. Second, the claimed EPO elicits the very same in vivo activity as natural EPO and, therefore, is suitable for use in EPO therapy procedures. Third, the claimed EPO increases hematocrit in mammals, as exemplified in Example 10 of the '422 patent. By reciting "therapeutically effective amount of human erythropoietin," the patentee thus demonstrated an intention to claim EPO that (1) causes the same in vivo biological effects as the natural EPO; and also (2) increases hematocrit.

The subsequent disclosure strengthens my view that the district court correctly construed the "therapeutically effective" limitation.

> A preferred method for administration of polypeptide products of the invention is by parenteral (e.g., IV, IM, SC, or IP) routes and the compositions administered would ordinarily include *therapeutically effective* amounts of product in combination with acceptable diluents, carriers and/or adjuvants. . . . Effective dosages are expected to vary substantially depending upon the condition treated but therapeutic doses are presently expected to be in the range of 0.1 (~70) to 100 (~7000 U) μg/kg body weight of the active material.

'422 patent, col. 33, ll. 41-52 (emphasis added). In the only part of the specification where the term "therapeutically effective" actually appears, the patentee uses the term in the ordinary sense of the phrase to mean promoting "healing" or "curing." That is, the patentee teaches the preferred amount of EPO product and a preferred method of administration for a patient suffering from a disorder characterized by a low red blood cell count. Inherently, the ultimate goal is to "heal" or "cure" the disorder. That healing is characterized by an increased red blood cell count, i.e., a higher hematocrit level.

Significantly, I note that the words "therapeutically effective" are conventionally employed in the pharmaceutical arts to indicate that the claimed pharmaceutical product has utility in the treatment of a human disease where such treatment tends to cause the "healing" or "curing" of the disease. The patentee, I think, intended to invoke that very convention. While the majority might be correct that the '422 patent is not necessarily limited to the exact class of patients described in the specification (as opposed to other blood disorders associated with low hematocrit levels), the district court correctly recognized that it would be "foolish to construe a term such as 'therapeutically effective,' without reference to a

class of patients for which the product is intended to be 'therapeutically effective.'" *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 237.

The specification further discloses various analogs of EPO at columns 35-36:

> In addition to naturally-occurring allelic forms of mature EPO, the present invention also embraces other "EPO products" such as polypeptide analogs of EPO and fragments of "mature" EPO. . . . Especially significant in this regard are those potential fragments of EPO which are elucidated upon consideration of the human genomic DNA sequence of FIG. 6, i.e., "fragment" of the total continuous EPO sequence which are delineated by intron sequences and which may constitute distinct "domains" of biological activity. It is *noteworthy that the absence of in vivo activity for any one or more of the "EPO products" of the invention is not wholly preclusive of therapeutic utility (see, Weiland, et. al., supra) or of utility in other contexts, such as in EPO assays or EPO antagonism.*

'422 patent, col. 35, ll. 34-37; col. 36, ll. 4-14. The majority mistakenly relies on this disclosure to support its view that the "therapeutically effective" means merely capable of triggering *any* in vivo biological activity, regardless of degree. Correctly read, the emphasized passage plainly concerns only analogs of EPO, not the EPO of claim 1. That is, the full disclosure teaches that *analogs* of EPO may offer therapeutic utility even though they may not have in vivo activity. The emphasized sentence says nothing about the *claimed* EPO and hence cannot be relied upon to construe the "therapeutically effective" limitation.

The prosecution history further confirms that "therapeutically effective" connotes more than simply eliciting any cited in vivo biological effect. The district court emphasized that

during prosecution of the '422 patent, the patentee differentiated its invention from natural EPO, which also elicits the aforementioned biological activity, on the basis that the latter was not available in large enough quantities to treat patients, i.e., help cure their diseases. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 239. Likewise, during the prosecution of the Application No. 07/113,178, a parent application of the '422 patent which itself issued as United States Patent No. 5,441,868, the patentee distinguished the claimed EPO from the prior art, emphasizing that the claimed EPO could be used as a therapeutic product to treat humans with blood disorders characterized by a low red blood cell count whereas the prior art EPO could not. In particular, the patentee stated:

> [N]aturally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proved to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts.

In so differentiating the claimed EPO from the prior art, the patentee said that the claimed EPO is capable of doing more, i.e., the claimed EPO "heals" or "cures" anemia and other such disorders by raising a patient's red blood cell count.

Thereafter, during the prosecution of the Application No. 08/100,197, a continuation of Application No. 07/113,178 discussed above, the examiner objected that "Claim 62 is vague and indefinite because it is unclear what the claimed composition is required to be 'effective' for." In response, after quoting column 33, lines 11-28, which includes a description of the in vivo biological effects, the "increasing hematocrit" language, and various diseases treatable with the claimed invention, the patentee again explained that the

claimed EPO could be used to treat, (i.e., "heal" or "cure"), various blood disorders:

> It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be therapeutically effective. A person of skill in the art would understand that the amount of erythropoietin necessary to achieve these *defined therapeutic results* would vary for each use. However, clinicians can readily determine the "therapeutically effective" amounts for each condition, and indeed for each patient. Application submits that the claim language "therapeutically effective amount" is commonly used in this type of case where the product is usable to treat various conditions.

(emphasis added). Accordingly, I must conclude that the district court's construction of the "therapeutically effective" limitation comports with the patentee's own repeated descriptions of the claimed invention. It is exactly the way a skilled artisan would interpret the patent, as the district court held.

II.

Regarding possible anticipation of the invention of the '422 patent by the Goldwasser reference, the district court set forth very specific reasons why none of the in vivo biological effects mentioned in the Goldwasser reference (i.e., an increase reticulocytes, an increase in plasma iron clearance, and red cell mass changes) demonstrated therapeutic effectiveness. HMR does not contend that the district court clearly erred. Rather, it merely asserts that all of these biological results fall under its proposed claim construction for the term "therapeutically effective amount," which is any amount of EPO that elicits any in vivo biological effect, even if not accompanied by an increased hematocrit. Because I think that the district court correctly rejected HMR's proposed construction and properly construed "therapeutically effective" to

mean "healing" or "curing," HMR's validity challenge necessarily fails. While all of the results described in the Goldwasser reference represent in vivo biological responses, none demonstrate that the subject anemic patients were even partially "healed" or "cured." In fact, Dr. Goldwasser himself considered his study a failure because the patients' hematocrit levels did not increase. I therefore conclude that the district court correctly found that the Goldwasser reference does not anticipate claim 1 of the '422 patent. Clear error has not been shown. We should therefore affirm the judgment as to validity.

III.

This litigation has already dragged on for almost ten years, yet the end is nowhere in sight. The majority again remands this case to the district court, this time for a re-adjudication of whether the Goldwasser reference anticipates claim 1 of the '422 patent in light of its revised construction of "therapeutically effective." The district court, as a result, will conduct further proceedings and render a third opinion. Inevitably, at least one party will appeal that judgment, prompting a third review by this Court. We, in turn, will issue another opinion, perhaps even remanding the case a third time. The district court, however, has yet to decide whether to grant an injunction, the specific relief sought by the patentee. Presumably, after our decision in that potential third appeal, the district court would conduct a trial or hearing on that issue and reach another decision, which will likely be appealed by one or both of the parties. We consequently would hear a fourth appeal and issue a fourth decision, which could involve yet another remand. When will it end? Ironically, the patents in dispute may expire before this litigation concludes.

Moreover, since the majority holds that other asserted patents are not invalid and are literally infringed by HMR 4396, (and here I agree), the district court likely will enter an injunction precluding appellants from marketing HMR 4396

until the expiration of at least the '698 and '349 patents. Prolonging this litigation seems futile when, in the end, an injunction will likely issue regardless of how "therapeutically effective" is construed or whether claim 1 of the '422 patent is invalid.

APPENDIX B

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 97-10814-WGY

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC. and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

MEMORANDUM AND ORDER

YOUNG, C.J. October 15, 2004

I. INTRODUCTION

This patent infringement action concerns patents held by Amgen, Inc. ("Amgen"), relating to the manufacture of a recombinant (genetically engineered) DNA[1] product, known as epoietin alfa,[2] that is similar to natural erythropoietin ("EPO"), a hormone that stimulates production of red blood cells, and is useful in, among other things, treating patients who need of blood transfusions and suffer from blood composition disorders such as hemophilia, anemia, and sickle cell disease. This product and this case are not new to the public or to this Court. The case began brewing in 1997, when Amgen filed a declaratory judgment in the United States District Court for the District of Massachusetts against

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[1] "DNA" is short for "deoxyribonucleic acid."

[2] This product is sold under the trademark EPOGEN®.

Defendants Hoechst Marion Roussel, Inc.[3] and Transkaryotic Therapies, Inc. (collectively "HMR/TKT") claiming that three of its patents were infringed by HMR/TKT's human EPO product, "HMR 4396," produced from the R223 cell line grown in culture. *See Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 106 (D. Mass. 1998). In 1999, Amgen amended the complaint to include two other patents. *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 96-98 (D. Mass. 2001) ("*Amgen I*"). A lengthy jury-waived trial ensued. It commenced in May 2000 and lasted twenty-three days over the course of four months. *Id.* at 78. Not surprisingly, HMR/TKT appealed this Court's decision, *Amgen I*, 126 F. Supp. 2d 69. In *Amgen Inc.* v. *Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) ("*Amgen II*"), the Federal Circuit affirmed a majority of this Court's findings and rulings but vacated and remanded a few issues to this Court. *Id.* at 1358. This memorandum and order addresses those issues on remand, some of which have already been decided by the Court and announced to the parties, thus requiring only a brief review.

II. BACKGROUND: PROCEDURAL AND SUBSTANTIVE HISTORY

A. The Patents at Issue

There were originally five patents at issue in this case. Only four, however, remain on remand. The patents and claims now at issue are: Claim 1 of U.S. Patent No. 5,955,422 (issued Sept. 21, 1999) ("'422 patent"); Claims 2-4 of U.S. Patent No. 5,621,080 (issued Apr. 15, 1997) ("'080 patent"); Claims 4-9 of U.S. Patent No. 5,618,698 (issued Apr. 8, 1997) ("'698 patent"); and Claims 1, 3, 4, 6, and 7 of U.S.

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[3] Hoechst Marion Roussel, Inc. is now known as Aventis Pharmaceuticals, Inc.

Patent No. 5,756,349 (issued May 26, 1998) ("'349 patent"). *Amgen I*, 126 F. Supp. 2d at 79; *Amgen II*, 314 F.3d at 1320.[4]

Although the patents vary, they all share a common disclosure and identical specifications. *Amgen I*, 126 F. Supp. 2d at 79. For ease of reference, the Court cites to the specification found in the '933 patent, which is identical to the specification of the patents in dispute on remand. '933 Patent, Ex. 1.[5]

B. The Technology

As *Amgen I* set out the basics of the underlying technology in detail, only a brief summary is provided here. EPO is a naturally occurring hormone that controls erythropoiesis, the production of red blood cells in bone marrow. '933 Patent, Ex. 1, col. 5: 39-67. Erythropoiesis occurs continuously to offset cell destruction. *Id.* It enables a sufficient (but not excessive) amount of red blood cells to be available in the blood to provide tissue oxygenation. *Id.* Hemoglobin is the protein in the red blood cells that actually transports the oxygen. *Amgen I*, 126 F. Supp. 2d at 98. The amount of hemoglobin correlates to the amount of oxygen. *Id.* Hematocrit, which indicates the relative proportion of red blood cells to the total volume of blood, measures the ability of the blood to supply oxygen to the body. *Id.* Thus, generally an increase or

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[4] The fifth patent involved in *Amgen* I was U.S. Patent No. 5,547,933 (issued Aug. 20, 1996) ("'933 patent"). Since this Court's ruling that the '933 patent was invalid for indefiniteness under 35 U.S.C. § 112, ¶ 2 was upheld on appeal, *Amgen II*, 314 F.3d at 1342, that patent will not be addressed in this memorandum and order.

[5] Because many of the exhibits from the first trial were used in the second trial and the numbering system was simply continued in the second trial, the Court will not designate from which trial the exhibits came but instead simply refer to the trial exhibit number. When citing testimony, however, the Court will refer to the second trial as the "remand trial" and cite it as "R. Trial," while the first trial will simply be cited as "Trial."

decrease in hematocrit equates with an increase or decrease in the ability to supply oxygen to the body. *Id.* Under normal conditions, a person has a hematocrit of about forty-five to fifty, which means forty-five to fifty percent of the blood is made up of red blood cells. *Id.*

EPO is produced in the kidney and liver. Therefore, patients with chronic renal failure lack normal levels of EPO and suffer from anemia. *Amgen II*, 314 F.3d at 1321. Introduction of additional EPO into the patient's body can increase a patient's hematocrit level and sustain it at or near normal levels. *Id.* In other words, the blood is able to provide a steady supply of sufficient oxygen to the tissues. *Id.*; *Amgen I*, 126 F. Supp. 2d at 99.

Early attempts to obtain EPO from plasma or urine proved unsuccessful because the body only produces human EPO in very small amounts, '933 Patent, Ex. 1, col. 5: 54-58, and the techniques were very complicated and resulted in the collection of very small amounts of impure and unstable amounts of EPO, *id.* at col. 6: 60-65. Amgen is recognized as the pioneer in the production of a therapeutically effective amount of EPO via recombinant EPO ("rEPO") techniques. *See, e.g., Molecular Biology and Biotechnology: A Comprehensive Desk Reference* 108 (Robert A. Meyers ed., VCH Publishers 1995).

Dr. Fu-Kuen Lin ("Lin"), the named inventor of all the patents in issue, isolated and characterized DNA sequences encoding EPO from humans and monkeys. '933 Patent, Ex. 1, col. 13: 50-53. Lin determined the DNA sequence of human EPO and its predicted amino acid sequence. '933 Patent, Ex. 1, col. 10: 65-11: 2. Lin then produced large amounts of EPO by using recombinant DNA technology. *Id.* at col. 14: 23-29. In the patent specification, many methods of producing EPO are described. EPOGEN® is produced by the method described in Example 10, wherein human EPO is produced by introducing exogenous DNA into host Chinese hamster ovary

("CHO") cells. *Id.* at col. 25: 30-29: 7.[6] The rEPO that is produced has the same or similar amino acid sequences or primary structural conformation as that of naturally-occurring EPO. *Id.* at col. 29: 1-7. As a result, it possesses one or more the biological properties of naturally-occurring EPO but differs from natural EPO in its "glycosylation," that is, it has a different average carbohydrate composition. *Id.* at col. 10: 35-41.

HMR/TKT, in producing its human erythropoietin, HMR 4396 (also called Gene-Activated EPO "GA-EPO"), also uses recombinant technology. HMR/TKT, however, does not use a host cell from a non-human species but manipulates the ordinarily unexpressed human EPO gene where it naturally resides. *Amgen I*, 126 F. Supp. 2d at 102. In that way, the human EPO DNA material is endogenous to the human cell. *Id.* After introducing a promoter sequence, human EPO is expressed in a human rather than a hamster cell. *Id.*

C. The Federal Circuit's Decision

A brief review of the key rulings and findings that were affirmed and remanded on appeal follows:

1. Claim Construction

a. Affirmed

The Federal Circuit upheld all of the Court's claim constructions. *Amgen II*, 314 F.3d at 1320. Specifically, the Federal Circuit upheld this Court's construction that Amgen's claims do not limit the invention to using only exogenous

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[6] Amgen transfects CHO cells with a vector that contains both viral promoter DNA and the human EPO gene. '933 Patent, Ex. 1, col. 25: 58-61; *Amgen I*, 126 F. Supp. 2d at 102. Therefore, the human EPO DNA material is exogenous to the hamster host cell because it was removed from the cell in which it originated, placed in a vector, and reintroduced into a host cell. *Amgen I*, 126 F. Supp. 2d at 102. This is called heterologous recombination. *Id.*

DNA (as opposed to endogenous DNA). *Id.* at 1327. It also upheld this Court's determinations that (1) non-naturally occurring means "'not occurring in nature'"; (2) vertebrates are anything with "'a segmented bony or cartilaginous spinal cord' which obviously includes humans"; and (3) humans are a subset of mammals and mammals are a subset of vertebrates. *Id.* at 1327-28 (quoting *Amgen I*, 126 F. Supp. 2d at 85, 90-91). To that end, the Federal Circuit agreed that the specification indicates that the invention uses human DNA in human host cells in culture. *Id.*

The Federal Circuit also upheld the Court's determination that claim 1 of the '422 patent, claims 2, 3, and 4 of the '080 patent, and claims 1, 3, 4, and 6 of the '349 patent are product claims (not process claims) and thus are not restricted or defined by any method of production or any particular source, other than what is specifically excluded. *Amgen II*, 314 F.3d at 1329-30.

b. Remanded

Although all the terms that this Court construed in *Amgen I* under the principles of *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), were upheld, the Federal Circuit remanded to this Court the construction of the term "therapeutically effective."[7] *Amgen II*, 314 F.3d at 1354. This phrase was not considered by the Court to be in dispute during the first trial. In its written analysis, however, this Court interpreted the term. *Amgen I*, 126 F. Supp. 2d at 112; *see also id.* at 99. While interpreting a term to provide context for the discussion is proper when the term is not in dispute, the Federal Circuit determined that the term "therapeutically effective" actually was in dispute "because it is central to whether Goldwasser is properly considered prior art." *Amgen II*, 314 F.3d at 1353. Therefore, it remanded so this Court could construe "thera-

[7] The term "therapeutically effective" is found in claim 1 of the '422 patent and in claim 4 of the '080 patent.

peutically effective" pursuant to *Markman*. *Id.* at 1358. Since claim construction is matter of law, *Markman*, 517 U.S. at 386; *but see* Arthur R. Miller, *The Pretrial Rush to Judgment: Are the "Litigation Explosion," "Liability Crisis," and Efficiency Clichés Eroding Our Day in Court and Jury Trial Commitments?*, 78 N.Y.U. L. Rev. 982, 1087 (2003) (criticizing the decision in *Markman*), the Federal Circuit could have proceeded to construe the phrase itself. Where a word or phrase has not been first construed in the district court, the Federal Circuit follows the courteous and prudential path of first seeking claim construction below. Hon. Pauline Newman, Remarks at the American Law Inst.-Am. Bar Assoc. Panel on the Trial of a Patent Case (Sept. 18, 2003).

2. Infringement

a. Affirmed

The Federal Circuit affirmed this Court's ruling on summary judgment that claim 1 of the '422 patent is literally infringed. *Amgen II*, 314 F.3d at 1348. It also affirmed this Court's ruling that the '080 patent is not literally infringed by HMR/TKT's HMR 4396, *id.* at 1344-45, but that claims 1, 3, 4, and 6 of the '349 patent are literally infringed by it, *id.* at 1351-52.

b. Remanded

(1) The '080 Patent

After finding that HMR 4396 did not literally infringe claims 2, 3, and 4 of the '080 patent because HMR 4396 comprised only 165 amino acids, *Amgen I*, 126 F. Supp. 2d at 99-101, this Court held that HMR 4396 performed substantially the same function in substantially the same way to obtain substantially the same result as the EPO glycoprotein of claims 2 and 3 of the '080 patent, *id.* at 133. Therefore, it ruled that Amgen's '080 patent was infringed by HMR/TKT's product under the doctrine of equivalents. *Id.*

In response to HMR/TKT's argument that Amgen should be estopped from arguing equivalent infringement, this Court ruled that prosecution history estoppel did not apply because Amgen did not add the "mature amino acid sequence of Figure 6" limitation "in an attempt to overcome a rejection [or] to avoid prior art," but, instead, to "demonstrate that 'same invention' type double patenting did not apply,"—that is, to distinguish the '080 patent from the '933 patent. *Id.* at 134-35.

The Federal Circuit agreed that the amendment was made for this purpose but made clear that under *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 731 (2002) ("*Festo II*"), "'a narrowing amendment to satisfy *any* requirement of the Patent Act may give rise to an estoppel.'" *Amgen II*, 314 F. 3d at 1345 (quoting *Festo II*, 535 U.S. at 736) (emphasis added). Therefore, it held that the presumption of prosecution history estoppel applied. *Id.* at 1345. The Federal Circuit then vacated this Court's finding of equivalent infringement and remanded for an analysis based on the "narrow ways of rebutting the Supreme Court's presumption of estoppel" outlined in *Festo II*. *Id.* at 1345.

(2) The '698 Patent

On appeal, the Federal Circuit vacated and remanded this Court's ruling regarding infringement of the '698 patent because this Court had compared the accused device to the preferred or commercial embodiments of the patent instead of to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1347. Therefore, it remanded to this Court the question whether claims 4-9 of the '698 patent are infringed. *Id.*

(3) The '349 patent

Although this Court found that claims 1, 3, 4, and 6 of the '349 patent are literally infringed by HMR/TKT's 4396, it held that HMR/TKT did not literally or equivalently infringe claim 7, the process claim, of the '349 patent. *Amgen I*, 126

F. Supp. 2d at 122. The Court compared the accused process to the preferred embodiment in the claim and concluded that HMR/TKT's "process for producing erythropoietin differs markedly from that disclosed by Amgen's specification." *Id.* The Federal Circuit, as it did with the Court's holding of infringement of the '698 patent, vacated this ruling and remanded so that the Court could analyze infringement by comparing the accused process to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1350-51.

3. Inequitable Conduct

The Court's determination that HMR/TKT had not proven by clear and convincing evidence that the '933, '080, '349 and '422 patents were unenforceable due to inequitable conduct was affirmed on appeal. *Amgen II*, 314 F.3d at 1357-58.

4. Written Description, Definiteness, and Enablement

a. Affirmed

The Federal Circuit affirmed this Court's rulings that the '422, '080, and '349 patents are adequately described and enabled. *Id.* at 1337. In so ruling, the Federal Circuit explained that this Court "carefully considered these issues, finding in the end that HMR/TKT had not met its clear and convincing burden of proof." *Id.* Because the Federal Circuit found "no clear error in these factual determinations," and the parties did not allege any legal error, it reasoned that it would "not disturb [this Court's] holding that the asserted patents are not invalid for failure to meet the enablement requirement of § 112 ¶ 1." *Id.*

As mentioned in an earlier footnote, *see* note 3, *supra*, this Court held and the Federal Circuit affirmed that the '933 patent (specifically the claims requiring "glycosylation which differs") was invalid for indefiniteness under section 112. *Amgen I*, 126 F. Supp. at 156-57. Therefore, the '933 patent is not at issue on remand.

5. Anticipation and Obviousness

a. Affirmed

The Court's ruling that the asserted claims of the '080, '349, and '933 patents are not anticipated under 35 U.S.C. § 102 by the Sugimoto reference was affirmed by the Federal Circuit. *Id.* at 1320, 1356.[8] In affirming, however, the Federal Circuit made clear that the Court's determination that Sugimoto was not enabled was an error, though harmless, because the Court put the burden of proving enablement of Sugimoto on HMR/TKT when the burden of proving non-enablement should have been put on Amgen. *Id.* at 1356.[9]

b. Remanded

The Federal Circuit remanded, however, the Court's findings that Sugimoto does not anticipate claim 1 of the '422 patent stating that the "district court should consider whether claim 1 of the '422 patent is novel over Sugimoto in light of the court's new definition of 'therapeutically effective'" and be "mindful of the principle that source limitations cannot impart novelty to old compositions." *Id.* at 1356.[10] Addi-

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[8] In its opinion, the Federal Circuit affirmed this Court's finding that Sugimoto did not anticipate the '080, '933, '349, and '698 patents. *Amgen II*, 314 F.3d at 1320, 1356. This Court, however, never addressed the validity of the '698 patent. It concluded that the '698 patent was not infringed literally or equivalently at the close of Amgen's direct case. *Amgen I*, 126 F. Supp. 2d at 101. Therefore, whether Sugimoto anticipates the '698 patent is one of the issues addressed in this memorandum and order.

[9] The error was harmless because the Court, despite having concluded that Sugimoto was not enabled, "nevertheless conducted a full anticipation analysis" and found that "'none of the cited references disclose[s] each and every limitation of any of Amgen's individual claims'" of the '080, '933 and '349 patents. *Amgen II*, 314 F.3d at 1356 (quoting *Amgen I*, 126 F. Supp. 2d at 109).

[10] It is clear from *Amgen II* that Amgen may on remand argue that the '422 patent is not anticipated because Sugimoto is not enabled. *See*

tionally, the Federal Circuit remanded this Court's finding that the '422, '080, and '349 patents were not obvious in light of Sugimoto because this Court based its decision, in part, on the fact that it concluded that Sugimoto was not enabled. *Id.* at 1357. The Federal Circuit explained that under section 103, a reference need not be enabled to qualify as prior art. *Id.*

In *Amgen I*, this Court found that the asserted claims of the '080, '422 and '349 patents were not anticipated or rendered obvious by the Goldwasser reference. *Amgen I*, 126 F. Supp. 2d 112-17. The Federal Circuit remanded these findings for further proceedings given that "therapeutically effective" was not construed in accordance with *Markman*. *Amgen II*, 314 F.3d at 1354. As mentioned above, it directed the Court to construe the term and determine whether Goldwasser invalidates any of the asserted patents under 35 U.S.C. § 102(a) or § 103 in light of the Court's construction. *Id.* at 1354.

D. Procedural and Substantive History Since *Amgen II*

The Federal Circuit's decision issued on January 6, 2003. This Court received the action on remand on March 13, 2003 [Doc. No. 653], and it held a status conference on April 16, 2003 [Doc. No. 657]. On May 16, 2003, Amgen moved for: (1) judgment under Federal Rule of Civil Procedure 52(c) that claims 2-4 of the '080 patent were infringed under the doctrine of equivalents [Doc. No. 659]; (2) summary judgment of infringement of claims 4-9 of the '698 patent [Doc. No. 663]; (3) judgment pursuant to Rule 52(c) that claim 1 of the '422 patent and claim 4 of the '080 patent are valid [Doc. No. 670]; and (4) judgment pursuant to Rule 52(c) that claims 1, 3, 4, 6, and 7 of the '349 patent are valid and that claim 7

Amgen II, 314 F.3d at 1354-57. The burden of proving Sugimoto's non-enablement, however, rests with Amgen. Moreover, Amgen must present more evidence than that adduced in the first trial as the Federal Circuit made clear that the evidence from the first trial was insufficient to prove non-enablement.

of the '349 patent is infringed [Doc. No. 674]. HMR/TKT simultaneously moved for: (1) judgment that Amgen is estopped from asserting infringement of the '080 patent pursuant to the doctrine of equivalents [Doc. No. 678]; (2) judgment that claim 1 of the '422 patent is invalid as anticipated [Doc. No. 682]; (3) judgment pursuant to Rule 52(c) that the asserted process claims of the '698 patent and '349 patents are not infringed [Doc. No. 686]; and (4) judgment that the '422, '080, and '349 claims are invalid for obviousness [Doc. No. 690].

The memoranda in support of and in opposition to these motions raised additional issues that are reviewed in this opinion. They are described briefly below.

In its opposition to Amgen's renewed motion for summary judgment of infringement of the '698 patent,[11] HMR/TKT argued, among other things, that Amgen's proposed construction of the words "DNA encoding" found in claims 4 and 6 of the '698 patent is incorrect. HMR/TKT's Mem. in Opp'n re '698 [Doc. No. 700] at 7-8. Second, HMR/TKT argued that in claims 4 and 6 of the '698 patent, Amgen set forth a step-plus-function claim in referring to the "steps of . . . growing, under suitable nutrient conditions" and that an assessment of whether HMR/TKT infringed this aspect of the claim must focus on a comparison between HMR/TKT's process for growing and the process for growing described by Amgen in the specification. *Id.* at 9. Finally, HMR/TKT argued that even if there is literal infringement here, it can justifiably invoke the defense of the reverse doctrine of equivalents. *Id.* at 13.[12]

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[11] During the first trial, this Court found in favor of HMR/TKT on equivalent and literal infringement of the '698 patent after Amgen presented its case but before HMR/TKT had the opportunity to present its case on this issue.

[12] HMR/TKT also attempted to argue that the '698 patent should be declared unenforceable because it was obtained as a result of inequitable conduct. This Court, during the pretrial conference on September 24,

With regard to claim 7 of the '349 patent, HMR/TKT made four "new" arguments, two of which are very similar to those made in conjunction with the '698 patent. First, HMR/TKT contended that its process does not infringe claim 7 of the '349 patent when considered in light of its proposed claim construction of "DNA encoding." HMR/TKT's Mem. in Support re '698/'349 [Doc. No. 687] at 8-9. Second, HMR/TKT argued that its process does not infringe claim 7 of the '349 patent because claim 7 is a step-plus-function limitation; and, as such, HMR/TKT's process does not literally infringe the "step of culturing" found in claim 7 because it does not involve the culturing procedures set forth in Amgen's specification. *Id.* at 12-15. Third, HMR/TKT claimed that its process does not infringe the process claim under the reverse doctrine of equivalents. *Id.* at 15-18. Fourth and lastly, HMR/TKT argued that if the Court construes the term "DNA encoding" as Amgen urges, then the validity of the asserted claim of the '349 patent is called into question. *Id.* at 12.

Amgen, in response, did not dispute that "DNA encoding" needs to be construed by the Court. *See, e.g.*, Amgen's Reply re '698 [Doc. No. 731] at 6-10. It did, however, assert that HMR/TKT should not be allowed to make its "new" arguments relating to step-plus-function and the reverse doctrine of equivalents given the procedural posture of the case.[13] *See, e.g., id.* at 10-15.

2003, ruled that HMR/TKT could not put on any evidence of inequitable conduct relating to the '698 patent because it was "satisfied that the pleadings, the pretrial documents early on as to '698 did not frame that issue for trial." 9/24/03 Pretrial Conf. Tr. at 26: 4-9.

[13] Therefore, these memos requested that the Court (1) construe "DNA encoding"; (2) decide whether HMR/TKT is allowed to make its step-plus-function arguments at this stage and if yes, determine whether the asserted claims of the '349 and '698 patents are step-plus-function claims; and (3) determine whether HMR/TKT can argue the reverse doctrine of equivalents with respect to the '698 and '349 patents for the first time on remand and if so, whether this argument has merit.

On July 29, 2003, this Court held a *Markman* hearing regarding those terms in dispute and in need of construction and considered other pending motions, including motions for summary judgment. At the end of the *Markman* portion of the hearing, the Court tentatively construed the terms "DNA encoding" and "therapeutically effective," providing two constructions for the latter, one being an alternate. 7/29/03 Hr'g Tr. at 55: 1-56: 23. It then continued to hear argument. At the end of the day, the Court noted that it would determine whether the asserted claims of the '698 and '349 patents were step-plus-function claims at a later date. *Id.* at 176: 1-10. It then continued the motion hearing to July 31, 2003. *Id.* at 176: 11-15.

During a hearing two days later, the Court retracted the alternative construction and reiterated its primary "working construction," retaining its right to revise it after a more careful review of the claims, specification, and prosecution history. 7/31/03 Hr'g Tr. at 87: 5-88: 7. Additionally, it ruled that claims 4 and 6 of the '698 patent and claim 7 of the '349 patent were not step-plus-function claims pursuant to 35 U.S.C. § 112. *Id.* at 88: 8-89: 9. It then denied Amgen's motion for summary judgment of infringement of the '698 patent, citing Arthur Miller's recent article, *The Pretrial Rush to Judgment. Id.* at 89: 23-90: 25; *see* Miller, *supra.* The Court took everything else under advisement and set the final pretrial conference for September 18, 2003. *Id.* at 91: 25-92: 2.

On August 5, 2003, the Court entered an order regarding the pending motions. [Doc. No. 740]. It denied HMR/TKT's motions for summary judgment with respect to the validity of the asserted claims of the '422, '080 and '349 patents. Order of 8/5/03 at 1. It denied in part and allowed in part Amgen's motions, under Rule 52(c), for judgment that claim 1 of the '422 patent and claim 4 of the '080 patent are valid and that claims 1, 3, 4, 6, and 7 of the '349 patent are valid. *Id.* Because HMR/TKT did not dispute that the '080 and '349

patents are not anticipated by Goldwasser and that the '349 patent is not rendered obvious by Goldwasser, the Court allowed Amgen's motions with respect to these matters. *Id.* at 1-2. Specifically, the Court held that claim 4 of the '080 patent is not anticipated by Goldwasser and that claims 1, 3, 4, 6, and 7 of the '349 patent are not anticipated or rendered obvious by Goldwasser. *Id.* at 2. Because Amgen did not have the opportunity to rebut HMR/TKT's remaining validity arguments concerning the '422, '080, and '349 patents during trial in 2000, the Court stated that Amgen would have that opportunity at the October trial. *Id.*

On September 18, 2003, the Court held a final pretrial conference. After explaining that this case will not "turn into a patent version of Penelope's robe," in other words, that the Court and the parties were "not going to unravel anything [that the Court has] woven thus far which has not been unraveled by a higher court," the Court made the following findings and rulings. First, it ruled that it would hear and take evidence on the reverse doctrine of equivalents as it related to the '698 patent and that HMR/TKT could address other patent defenses. 9/18/03 Final Pretrial Conf. Tr. at 6: 4-16. Second, it ruled that Amgen had met its burden (outlined in *Festo II*) of proving that the prosecution history does not estop it from arguing equivalent infringement with regard to the '080 patent and it affirmed its earlier finding that HMR/TKT infringes claims 2-4 of the '080 patent. *Id.* at 7: 17-8: 5. It explained that it would issue a full opinion at a later date but that it might have to revisit the *Festo* issue due to the rapidly developing law in that area. *Id.* at 7: 19-25. The Court then turned to the '349 patent and explained that it would allow Amgen to put on rebuttal evidence as to the matter of obviousness and Sugimoto only and it made clear that the Court would not accept other evidence from HMR/TKT regarding the '349 patent. *Id.* at 8: 12-19, 16: 5-6 ("As far as evidence goes, '349 is in the can and I'm done with it."). The Court then issued a revised claim construction of

"therapeutically effective" based on a more thorough analysis of the claims, specification, and prosecution history. *Id.* at 9: 3-10: 25. The Court mentioned, however, that this revision may have made the third sentence of the construction unnecessary and, therefore, reserved its right to further consider the proper construction. *Id.* at 10: 21-25. It directed the parties to try the case based on the construction it had just issued along with a construction that eliminated the third sentence. *Id.* at 11: 1-5. The pretrial conference was continued until September 24, 2003. *Id.* at 30: 22-23.

During the further pretrial conference, the Court reviewed the issues to be tried and outlined the procedure for trial and the parameters for the introduction of evidence and expert testimony. *See* 9/24/03 Final Pretrial Conf. Tr. After the Court provided both parties with an opportunity to be heard on the subject, pursuant to Federal Rule of Civil Procedure 53(b)(1), the Court appointed Michele D. Beardslee as Special Master, beginning January 1, 2004, to assist the Court in research, analysis, and drafting of the forthcoming opinion. Order re Special Master [Doc. No. 801]; *see also* 11/07/03 Beardslee Aff. [Doc. No. 799].[14] The trial on remand was set to commence on October 7, 2003. 9/24/03 Final Pretrial Conf. Tr. at 40: 23.

On October 30, 2003, the Court issued an opinion supporting its ruling that Amgen had successfully rebutted the presumption of prosecution history estoppel as outlined in *Festo II* and, therefore, was not estopped from asserting

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[14] *See generally* Hon. Shira A. Scheindlin & Jonathan M. Redgrave, *Revisions in Federal Rule 53 Provide New Options for Using Special Masters in Litigation*, N.Y. St. B.A.J., Jan. 2004, at 10, *reprinted sub. nom. The Evolution and Impact of the New Federal Rule Governing Special Masters*, Fed. Law., Feb. 2004, at 35.

equivalent infringement of the '080 patent. *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126 (D. Mass. 2003) ("*Amgen III*").[15]

The remanded trial lasted nine days over the course of four and a half weeks.[16] All the remaining issues—those remanded to the Court from the Federal Circuit and those raised by the parties in the course of this remanded trial—are addressed herein.[17]

III. CLAIM CONSTRUCTION

As expounded in great detail in *Amgen I*, this Court strongly believes in the importance of construing patent claims without regard to the alleged infringement issues. *Amgen I*, 126 F. Supp. 2d at 80-81; *MediaCom Corp.* v. *Rates Tech., Inc.*, 4 F. Supp. 2d 17, 21-24 (D. Mass. 1998); *see also* Anthony R. Zeuli & Rachel Clark Hughey, *Avoiding Patent Claim Construction Errors: Determining the Ordinary and Customary Meaning Before Reading the Written Description*,

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[15] While the reasoning need not be rehashed in this memorandum and opinion, the Court takes this opportunity to note a few typographical errors in the decision. At the following pages, the word "urinary" was inadvertently added where it should not have been: 154 ("urinary" is used five times in note 39 and should be deleted); 157 (the word "urinary" is used right before note 41 and should be deleted). As will be noted, the word "urinary" is used in many other places throughout the opinion. These uses of the word should remain. These errors do not in any way change the result of that opinion. Correction of them, however, makes the opinion more accurate.

[16] During the remanded trial, Amgen moved for Judgment Pursuant to Rule 52(c) that claims 4-9 of the '698 patent were infringed and not invalid under 35 U.S.C. § 112 [Doc. No. 778]. The Court did not rule on this motion but instead deferred entering judgment until all of the evidence had been presented. *See* Fed. R. Civ. P. 52(c). The Court's final decisions regarding infringement and validity of the '698 patent will be explained in detail below.

[17] Previous decisions by the Court, such as claim constructions, will be explained in this memorandum.

Fed. Law., June 2004, at 29. One way to avoid conflating issues of fact and law and to ensure division between the fact finding and law explaining roles in a patent case is to hold the *Markman* hearing prior to and separate from the summary judgment motion hearing. Although (as mentioned above) this Court held the *Markman* hearing for the trial on remand on the same day as the summary judgment motions hearing, it kept the hearings independent of one another by separating the hearing into two parts. The first part dealt with claim construction. Then the Court held a recess, issued its preliminary constructions, and moved on to the summary judgment motions hearing.

The Court followed its usual procedure in conducting the *Markman* hearing. The Court entertained oral argument from counsel for each party. Counsel referred the Court to the relevant portions of the patent, specification, and prosecution history. Demonstrative exhibits were presented and references were made to certain expert testimony, but extrinsic evidence was not admitted.

At the conclusion of the *Markman* portion of the hearing the Court interpreted "therapeutically effective" and "DNA encoding"—cautioning that they were "working constructions"—and held off deciding whether the asserted claims of the '349 and '698 patent were step-plus-function claims. The Court then announced during the July 31, 2003 hearing that it did not construe the asserted claims of the '349 and '698 patents as step-plus-function claims. During the pretrial conference on September 18, 2003, after the Court had engaged in a more careful review of the patents, specification, and prosecution history, the Court issued a revised claim construction for "therapeutically effective." The final claim constructions are reproduced and explained below.[18]

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[18] While the focus of the *Markman* hearing was on the patents, specification, and prosecution history, the Court writes now with the benefit

A. "Therapeutically Effective"

1. Background

The term "therapeutically effective" is contained in claim 1 of the '422 patent and claim 4 of the '080 patent.[19] As mentioned above, although this phrase was not construed during the first trial, in determining whether prior art anticipated the '422 and '080 patents, the Court interpreted the term to mean an increase in hematocrit:

> Such evidence [of e.g., increased erythroid marrow stimulation] should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged. Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness, Dr. Goldwasser's study, which revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO.

Amgen I, 126 F. Supp. 2d at 112; *see also id.* at 99 ("The therapeutic effectiveness or benefit of an erythropoietin preparation is shown by demonstrating a correction in anemia by increasing and maintaining the hematocrit of a patient to normal or near normal levels.").

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of having presided over the entire second trial. Unsurprisingly, both parties continued to present arguments regarding construction throughout the trial, weaving in arguments regarding validity. The Court, however, construed the terms before the re-trial and, therefore, the arguments and intrinsic evidence addressed in this memorandum regarding construction of these terms stem from these data provided before the re-trial.

[19] The Federal Circuit refers to the term "therapeutically effective." The Court notes, however, that claim 1 of the '422 patent and claim 4 of the '080 patent actually recite a "therapeutically effective *amount*" of either "human erythropoietin" or "an erythropoeitin glycoprotein product," respectively. '422 and '080 Patents, Ex. 1 (emphasis added).

The Federal Circuit, in addition to remanding so that the Court could construe the term pursuant to *Markman*, provided some guidance. It agreed that the "endgame in the treatment of chronically anemic patients is to increase the hematocrit," but pointed out that the term should be construed in light of the specification. *Amgen II*, 314 F.3d at 1353. It stated, however, that the "specification appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy." *Id.* (citing '933 Patent, col. 33: 19-31). It pointed out that Amgen was arguing that one skilled in the art would construe "therapeutically effective" as "increasing and maintaining the patient's hematocrit to normal or near normal levels," but that "the relevant question is not whether one of ordinary skill would so understand the term, but whether that term should be limited based upon the express disclosure in the specification." *Id.* at 1353-54 (citing *CCS Fitness* v. *Brunswick Corp.*, 288 F.3d 1359, 1367 (Fed. Cir. 2002) ("[A] claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention.")). The Federal Circuit stated that it appeared that the term "therapeutically effective" encompassed the list of effects described in the specification and noted that if the Court also held this to be true, then the Goldwasser study may indeed invalidate some of the claims at issue in this case under 35 U.S.C. § 102(a) or § 103. *Id.* at 1354 ("If the claim term 'therapeutically effective' encompasses the patient responses described in the specification, *as it appears to us it does*, then the Goldwasser study may constitute invalidating prior art under § 102(a) or § 103 even if he did not achieve his intended result.") (emphasis added)). Therefore, it vacated this Court's determination that Goldwasser did not constitute prior

art[20] and ordered this Court to construe the term and thereafter determine whether Goldwasser invalidates any of the asserted patents. *Id.*

2. The Claims at Issue

The actual words of the claims are as follows:

> *'422 Claim 1*: A pharmaceutical composition comprising a *therapeutically effective* amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, where insaid erythropoietin is purified from mammalian cells grown in culture.

'422 Patent, Ex. 1, col. 38: 36-41 (emphasis added).[21]

> *'080 Claim 4*: A pharmaceutical composition comprising a *therapeutically effective* amount of an erythropoietin glycoprotein product according to Claim 1, 2, or 3.

'080 Patent, Ex. 1, col. 38: 51-53 (emphasis added).

3. Summary of the Parties' Arguments

Amgen urges adoption of the ordinary meaning of "therapeutically effective" given by those skilled in the art. Amgen's Mem. in Support re '422/'080 [Doc. No. 671] at 7. Specifically, it argues that (1) expert testimony shows that the ordinary meaning of "therapeutically effective" is "sufficient to produce a sustained increase in hematocrit," and that the term requires a therapeutic—not merely biological—effect; (2) the other effects listed in the specification, to which the Federal Circuit referred, are known biological effects of EPO, not the intended therapeutic effects; (3) the specification

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[20] The Court came to this conclusion because it found that the Goldwasser study was a failure.

[21] Although the Court did not receive evidence during the *Markman* hearing, for the sake of unity throughout this decision, citations to the patents are made to what was identified as Trial Exhibit 1 ("Ex. 1") (which contains the common specification and recitation of all the claims).

taken as a whole supports the plain meaning of "therapeutically effective," and that no special meaning was given to the term; (4) the prosecution history shows that Amgen specifically noted that its invention shares the same in vivo biological activity as naturally occurring human EPO, but differentiated its invention from prior art by pointing out that human recombinant EPO (unlike naturally-occurring human EPO) is not a viable, effective human therapeutic product; and (5) the doctrine of claim differentiation requires that this term have a different meaning than the recitation of EPO's biological activities. *Id.* at 8-17. In its reply memorandum, Amgen also argues that the dictionary definition of the term supports its asserted meaning. Amgen's Reply re '422/'080 [Doc. No. 730] at 5-6.

HMR/TKT, on the other hand, argues that the Federal Circuit made clear that it believed that the term "therapeutically effective" encompasses all of the effects set forth in the specification described. HMR/TKT's Mem. in Opp'n re '422/'080 [Doc. No. 702] at 5. Thus, it argues, the term encompasses those effects observed in the Goldwasser study. *Id.* at 6. Moreover, it asserts that Amgen is trying to import limitations from the specification to make the claims require an increase in the hematocrit levels when the claims contain no language indicating such a requirement and the specification language itself is actually inconsistent with such a requirement. HMR/TKT points to the same section of the specification as did the Federal Circuit did to make its point:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates *they are conspicuously suitable for use in erythropoietin therapy procedures* practiced on mammals, including humans, *to develop any or all of the effects herefore attributed in vivo to EPO*, e.g., stimulation of reticulocyte response, development of ferrokinetic effects . . . erythrocyte mass changes, stimulation of hemoglobin

> C syntheses . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

Id. at 13 (quoting '933 Patent, Ex. 1, col. 33: 19-31). This, HMR/TKT asserts, makes clear that "erythropoietin therapy procedures" include procedures that "develop any or all of the effects heretofore attributed in vivo to EPO," and, therefore, "therapeutically effective amount" includes any or all of the effects listed in this portion of the specification—which, HMR/TKT argues, are defined in terms of biological effects. *Id.* at 14. HMR/TKT further argues that Amgen is trying to rely on isolated references of the specification to restrict the term meaning when these restrictions are not apparent in the plain language, and when the intrinsic record, as a whole, supports a broader interpretation. *Id.* at 16.

4. Discussion

While the Federal Circuit indeed mentioned that the term "therapeutically effective" appeared to encompass the biological effects listed within lines 19-31 of column 33, the Court notes that the Federal Circuit did not, in *Amgen II*, actually construe the term "therapeutically effective." *See Amgen II*, 314 F.3d at 1324 (noting that the Federal Circuit considers claim construction "afresh" on appellate review); *Bayer AG* v. *Biovail Corp.*, 279 F.3d 1340, 1349 (Fed. Cir. 2002) (noting that, notwithstanding its *de novo* review, "it would be premature for this court to engage in its own claim construction without . . . evidence of the meaning of the terms to one of skill in the art at the time of the invention"). On the contrary, the Federal Circuit remanded that task to this Court. To perform it properly, however, the Court must consider the prosecution history in addition to the claims and the specification—something that the Federal Circuit did not do. *See Amgen II*, 314 F.2d at 1324 ("To properly construe the claims, a court must examine the claims, the rest of the specification, and if in evidence, the prosecution history."); *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582

(Fed. Cir. 1996) ("[I]t is well-settled that, in interpreting an asserted claim, the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history."); *SRI Int'l* v. *Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1118 (Fed. Cir. 1985) (noting that a claim is construed in light of its language, the specification, and the prosecution history). Moreover, the Court must begin by determining what the plain and ordinary meaning of "therapeutically effective" is in order to determine whether Amgen has become its own lexicographer. *Intellectual Prop. Dev., Inc.* v. *UA-Columbia Cablevision of Westchester, Inc.*, 336 F.3d 1308, 1315 (Fed. Cir. 2003) ("Consulting the written description and prosecution history as a threshold step in the claim construction process, before any effort is made to discern the ordinary and customary meanings attributed to the words themselves, invites a violation of our precedent counseling against importing limitations into the claims." (quoting *Texas Digital Systems, Inc.* v. *Telegenix, Inc.*, 308 F.3d 1193, 1204 (Fed. Cir. 2002)) (internal quotation marks omitted)).

a. The Plain and Ordinary Meaning

Generally, it is the plain and ordinary meaning of the words—as defined by one skilled in the relevant art—that governs. *Vitronics*, 90 F.3d at 1582; Erik Paul Belt, *Federal Circuit Stresses Ordinary Meaning*, Nat'l L.J., Sept. 22, 2003, at S1. Amgen argues that the plain and ordinary meaning of the term "therapeutically effective" is "sufficient to produce a sustained increase in hematocrit." HMR/TKT argues, on the other hand, that the plain and ordinary meaning of "therapeutically effective" is not so restricted.[22] Inter-

[22] HMR/TKT argues that Amgen's position on this claim construction is inconsistent with its position on claim construction for all the other terms the Court has construed in the previous trial because Amgen here is seeking to limit the term's definition via the specification and prosecution

estingly, HMR/TKT never states what it believes the plain and ordinary meaning of the term to be—it only discusses the meaning of the term with reference to how it believes Amgen has so defined it in the specification and prosecution history.

Amgen, on the other hand, grounds its assertion of the plain and customary meaning of the disputed term upon expert testimony. This, however, is extrinsic evidence to which resort ought be had only "*if necessary.*" *Vitronics*, 90 F.3d at 1583 (quoting *Hormone Research Foundation, Inc.* v. *Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990)). Therefore, the Court does not begin by considering this evidence. Instead, it turns first to the dictionary and to technical treatises to decipher the plain and ordinary meaning of "therapeutically effective." *See id.* at 1584 & n.6 (noting that judges are free to consult technical treatises and dictionaries

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history. HMR/TKT's Mem. in Opp'n re '422/'080 at 12. While it is true that Amgen has previously argued to the Court that the terms of the claims were entitled to their broadest possible scope, it also consistently argued that the words of the claim should prevail. *Amgen I*, 126 F. Supp. 2d at 82. In essence, it is here arguing this again. The difference is that, here, Amgen is arguing that the claim language itself contains a term that has a limited definition and that resort to the specification and prosecution history is not necessary since the plain meaning of the term prevails. HMR/TKT, on the other hand, is seeking to "broaden" what Amgen argues is the plain meaning by pointing to the specification and prosecution history.

Ultimately, how the issue has been framed will not change the analysis because it is clear from the principles of claim construction that claims are construed in light of the specification and prosecution history. *Southwall Techs., Inc.* v. *Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("The prosecution history limits the interpretation of claim terms so as to exclude *any* interpretation that was disclaimed during prosecution.") (emphasis added) (citations omitted)). Whether the Court determines that the term is limited or broadened is irrelevant. The important determinations instead are: What is the plain and ordinary meaning of "therapeutically effective," and does the intrinsic evidence define the term differently than its plain and ordinary meaning?

in order to gain a better understanding of the claims and to interpret them, "so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents.").[23]

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[23] At first glance, the extrinsic evidence rule in *Vitronics* appears to create somewhat of a conundrum, in that it discourages resort to extrinsic evidence while at the same time urging courts to begin claim construction by considering the plain and customary meaning of a term *as understood by one skilled in the art*. How does a Court decipher the plain and customary meaning of a term as understood by one skilled in the art without resorting to extrinsic evidence about how one skilled in the art would construe the term?

The Federal Circuit is currently considering this question en banc. In granting a petition for rehearing en banc in *Phillips* v. *AWH Corp.*, 03-1269, -1286, the Federal Circuit asked for briefing on the following questions:

> 1. Is the public notice function of patent claims better served by referencing primarily to technical and general purpose dictionaries and similar sources to interpret a claim term or by looking primarily to the patentee's use of the term in the specification? If both sources are to be consulted, in what order?
>
> 2. If dictionaries should serve as the primary source for claim interpretation, should the specification limit the full scope of the claim language (as defined by the dictionaries) only when the patentee has acted as his own lexicographer or when the specification reflects a clear disclaimer of claim scope? If so, what language in the specification will satisfy those conditions? What use should be made of general as opposed to technical dictionaries? How does the concept of ordinary meaning apply if there are multiple dictionary definitions of the same term? If the dictionary provides multiple potentially applicable definitions for a term, is it appropriate to look to the specification to determine what definition or definitions should apply?
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> 3. If the primary source for claim construction should be the specification, what use should be made of dictionaries? Should the range of the ordinary meaning of claim language be limited to the scope of the invention disclosed in the specification, for example, when only a single embodiment is disclosed and no other indications of breadth are disclosed?

> 4. Instead of viewing the claim construction methodologies in the majority and dissent of the now-vacated panel decision as alternative, conflicting approaches, should the two approaches be treated as complementary methodologies such that there is a dual restriction on claim scope, and a patentee must satisfy both limiting methodologies in order to establish the claim coverage it seeks?
>
> 5. When, if ever, should claim language be narrowly construed for the sole purpose of avoiding invalidity under, *e.g.*, 35 U.S.C. §§ 102, 103 and 112?
>
> 6. What role should prosecution history and expert testimony by one of ordinary skill in the art play in determining the meaning of the disputed claim terms?
>
> 7. Consistent with the Supreme Court's decision in *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), and our *en banc* decision in *Cybor Corp.* v. *FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998), is it appropriate for this court to accord any deference to any aspect of trial court claim construction rulings? If so, in what circumstances, and to what extent?

Phillips, Order of July 21, 2004. Judge Rader, concurring in the granting of the petition, added the following:

> Is claim construction amenable to resolution by resort to strictly algorithmic rules, e.g., specification first, dictionaries first, etc.? Or is claim construction better achieved by using the order or tools relevant in each case to discern the meaning of terms according to the understanding of one or ordinary skill in the art at the time of the invention, thus entrusting trial courts to interpret claims as a contract or statute?

Id. (Rader, J., concurring).

This Court's approach is first to consider the plain and ordinary meaning as defined by dictionaries and technical treatises, and then to consider the file wrapper to determine what it communicates to the reader about the plain and customary definition of the term. It may provide clues as to how one skilled in the art would define the term or which dictionary or technical definition is adopted by those skilled in the art. Then again, it may clearly redefine the term and thus overrule the plain and ordinary meaning deciphered by the Court. Regardless, since the patent process is a public one, whatever definition is *clearly* supported in the file wrapper is the one that ought prevail, since this is the one on which the public relies. Thus, if a term supposedly has a specific technical meaning that cannot be

gleaned from general dictionaries and treatises or the file wrapper, but can only be ascertained from expert testimony, this specific meaning will not be adopted, given the *Vitronics* rule against resort to extrinsic evidence.

This Court's approach resolves the apparent conundrum by drawing a line between cognitive and investigative tasks. One can understand this process by analogizing claim construction to contract interpretation. When a judge interprets the meaning of a term in a run-of-the-mill contract, she is determining how an ordinary speaker of English would understand the term, in context, and she cannot look to extrinsic evidence unless there is some ambiguity. A dictionary constitutes extrinsic evidence of the "plain and customary" meanings that members of the relevant language community ascribe to various words, but it is also serves as a tool to enhance the judge's cognitive capacities, which capacities are then applied to the task of interpretation. In theory, at least, a judge interpreting a contract written in a foreign language would follow the same process, though she might want to gain some background understanding of the language from experts. Having acquired such background, she could then use foreign language dictionaries the same way she would use an English dictionary. Having acquired the additional cognitive capacity, the judge might find that a term's meaning is ambiguous, in which case the judge could turn to extrinsic evidence, say, of industry custom. In other words, the judge would then conduct an empirical investigation of the behavior of relevant actors.

One could thus regard the task of judges in patent cases as one of learning a number of "difficult" words in the English language, or as one of entering a new community of language. In either case, seeking "fluency" is different from determining what customs prevail in a particular "art," even if those customs involve the use of an otherwise ambiguous term. Having learned to "speak" the relevant "language" by consulting lay and technical dictionaries (and perhaps having acquired background understanding from experts), the judge can then apply these new cognitive capacities to determine whether, in context, the patent term is ambiguous. Finding that meaning, then, involves an application of the judge's enhanced cognitive abilities, not an investigation of empirical facts.

In reality, construction of patent claims does not work the same way that interpretation of foreign-language contracts does. In practice, judges interpreting foreign language contracts rely on experts to interpret them. *See, e.g.*, 1st Cir. R. 30(d) ("The court will not receive documents not in the English language unless translations are furnished."); *Ramos-Báez* v. *Bossolo-Lopéz*, 240 F.3d 92, 94 (1st Cir. 2001) (similar); *cf.* 35 U.S.C.

The dictionary definition of "therapeutic" is "[h]aving healing or curative powers," or "[o]f or relating to the treatment of disease or disorders by remedial agents or methods." *The American Heritage Dictionary* 1260 (2d college ed. 1985); W*ebster's Ninth New Collegiate Dictionary* 1223 (1984), attached as Tab X to Supp. App. [Doc. No. 735] to Amgen's Reply re '422/'080; *see also Chamber's Technical Dictionary* 844 (3d ed. 1961), attached as Tab W to Supp. App. to Amgen's Reply re '422/'080 ("Of, or pertaining to, the medical treatment of disease: remedial: curative"). The definition of therapeutics is "[t]he medical treatment of disease." T*he American Heritage Dictionary*, *supra*, at 1260. The dictionary definition of "effective" is "[h]aving an intended or expected effect" or "[p]roducing or designed to produce the desired impression or response." *Id.* at 439.

Based on these definitions alone, one would surmise that a "therapeutically effective" amount is one that produces heal-

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§ 371(c)(2) (requiring that an applicant filing a national stage application submit a copy of the international application (with certain exceptions), as well as translation into the English language of the international application). Every foreign language contract is treated as "ambiguous," because learning a new language would involve too dramatic an expansion of a judge's cognitive capacities, and an empirical investigation is the best that she can do (although once that investigation reveals which English translation is correct, the judge can then determine whether that translated document is ambiguous). The Federal Circuit has decided, however, that learning the meaning of technical terms in English, or mastering the language used by members of a community of English-speaking persons of ordinary skill in a particular art, does not reach that level. The task of claim construction falls on the "cognitive" side of the divide between expanding and applying cognitive capacities, on the one hand, and investigating empirical facts, on the other. Thus, only when application of the judge's newly acquired cognitive capacities determines that a term's meaning is ambiguous does she then turn to empirical investigation of the behavior of persons skilled in the art. She then uses dictionaries, expert testimony, and so on not as a cognitive tool, but as evidence.

ing or curing as it relates to medical treatment of disease.[24] This is, in essence, consistent with the definition that Amgen proposes. *See* Amgen's Mem. in Support re '422/'080 [Doc. No. 671] at 14 (arguing that the ordinary meaning is an amount sufficient to "cure or relieve a disease state" and "require[s] a meaningful benefit to the health of patients"). Amgen, however, goes further, asserting that the plain and ordinary meaning of "therapeutically effective amount," to one skilled in the art, taken in the context of this patent, is an amount that provides more than the biological effects of EPO and "produce[s] a sustained increase in hematocrit," because only this result provides a meaningful benefit to the health of patients suffering from anemia.[25] *Id.* at 7-8, 14. Neither the claims, the specification, nor the prosecution history, however, demonstrate clearly that the plain and ordinary meaning of the term to one skilled in the art involves an increase in hematocrit. Therefore, the Court begins with the assumption that the plain and ordinary meaning of "therapeutically effective amount" is one in line with that found in the dictionaries and treatises noted above—i.e., one that heals or cures as it relates to medical treatment of disease.

The next step is to look to the claims, specification, and prosecution history to see if Amgen redefined the term in the file wrapper. In addition, the Court will look to these sources to determine whether the file wrapper indicates clearly the types of patients for which this product is "therapeutically effective" and thus infuses the term with real meaning. In-

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[24] To heal means "[t]o restore to health, or soundness; cure." *The American Heritage Dictionary*, *supra*, at 599.

[25] This was the meaning of the term that this Court essentially adopted in its previous opinion. It was founded on expert testimony demonstrating that those skilled in the art would define "therapeutically effective"—as it relates to treating anemia—as an increase in hematocrit. Again, however, resort to such extrinsic evidence ought be had only "*if necessary*." *Vitronics*, 90 F.3d at 1583 (quoting *Hormone*, 904 F.2d at 1562).

deed, this is the elephant in the room. Without tackling this question, the term "therapeutically effective" or "therapeutically effective amount" is vague and meaningless. The public must know upon reading the patent what disease state is cured or healed by the product.[26] As the Federal Circuit pointed out, "indiscriminate reliance on definitions found in dictionaries can often produce absurd results. . . . One need not arbitrarily pick and choose from the various accepted definitions of a word to decide which meaning was intended . . . . The subject matter, the context, etc., will more often than not lead to the correct conclusion." *Renishaw PLC* v. *Marposs Societa per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) (quoting *Liebscher* v. *Boothroyd*, 258 F.2d 948 C.C.P.A. 1958)) (first alteration in original). Thus, the Court, in addition to determining whether Amgen has expanded or confined the meaning of the disputed term, will look to the file wrapper to clarify this ambiguity.

b. The Claims

"The name of the game is the claim." *Amgen I*, 126 F. Supp. 2d at 80 (quoting Giles S. Rich, *Extent of Protection and Interpretation of Claims—American Perspectives*, 21 Int'l Rev. Indus. Prop. & Copyright L. 497, 499 (1990)) (internal quotation marks omitted). Thus, the first step in claim construction is to look to the plain and ordinary meaning of the words of the patent claim to determine the meaning of a term. *Vitronics*, 90 F.3d at 1582; *Bell Communications Research, Inc.* v. *Vitalink Communications Corp.*, 55 F.3d 615, 619-20 (Fed. Cir. 1995); *Renishaw*, 158 F.3d at 1248 ("[T]he claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim. . . . [T]he resulting claim interpretation must, in the

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[26] As will be noted *infra*, it appears that the patent examiner also believed that the patent needed to address for what disease states the product was "therapeutically effective."

end, accord with the words chosen by the patentee to stake out the boundary of the claimed property.").

Do the claims redefine the plain and ordinary meaning of the terms used? Amgen asserts that the claims do not support HMR/TKT's argument that it has redefined the term to include the biological effects of EPO. Amgen asserts that because claim terms are construed to give each term meaning, *Lantech, Inc.* v. *Keip Mach. Co.*, 32 F.3d 542, 546 (Fed. Cir. 1994), the patent claims themselves distinguish between biological and therapeutic effects. Amgen's Reply re '422/'080 at 10. To make its point, it refers to claims 4 and 2 of the '080 patent.

> *'080 Claim 4*: A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.
>
> *'080 Claim 2*: An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

Amgen asserts that under the doctrine of claim differentiation, claim 4 of the '080 patent must not include any or all of the effects listed in the specification because otherwise claim 4 would be identical to that of claim 2. Specifically, it points out that claim 4 of the '080 patent requires "[a] pharmaceutical composition comprising a therapeutically effective amount" of EPO according to claim 1, 2, or 3. Amgen's Mem. re '422/'080 at 15-16. It then asserts that the claim 2 requires the "in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." Therefore, if "therapeutically effective" included the effects listed in the specification to which the Federal Circuit pointed, Amgen argues, it would include the in vivo

biological activity cited by claims 1, 2, or 3 of the '080 patent and render claim 4 of the '080 patent superfluous. *Id.* at 16.

As HMR/TKT urges, however, this argument is flawed because claim 4 concerns a *pharmaceutical composition* comprising a "therapeutically effective amount" of an *EPO* that happens to have the qualities described in claim 2. HMR/TKT's Opp'n re '422/'080 at 22. HMR/TKT correctly points out that claim 2 recites an isolated EPO glycoprotein and therefore refers to biological effects whereas claim 4 recites a pharmaceutical composition and involves therapeutic effects. *Id.* at 21-22. Hence, claim 2 would not be rendered superfluous if this Court construed "therapeutically effective" to include the biological effects listed in the specification. *Id.* at 22.

Another equally flawed argument is that claim 4, by encompassing claim 2 (in referring to a "therapeutically effective" amount of the product claimed in claim 2), indicates that a "*therapeutically effective* amount" is one that does more than cause the in vivo biological activities described in claim 2. After a careful review of the technology and its history, it is clear that this is not a correct reading of the claims. This review relied on extrinsic evidence, as is permissible under Federal Circuit precedent. *Vitronics*, 90 F.3d at 1584 (noting that a court may resort to extrinsic evidence and expert testimony to help it understand the technology); *Altiris, Inc.* v. *Symantex Corp.*, 318 F.3d 1363, 1371 (Fed. Cir. 2003) ("In this regard, the expert testimony serves the permissible purposes of aiding our understanding of the technology and in helping us view the patent through the eyes of the skilled artisan.").[27]

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[27] Amgen argues, based on *Altiris*, that it can rely on expert testimony to confirm the plain and customary meaning of the word as understood by one skilled in the art. HMR/TKT argues that Amgen is using the expert testimony to change the ordinary meaning of a claim term. HMR/TKT's

Before Amgen's invention, human EPO was known to elicit certain biological effects, but it was impossible to extract an efficient amount of it for use in treatment of patients with anemias and other low red blood cell disorders. Amgen invented a product, recombinant EPO, that had the same in vivo biological effects as natural EPO but differed in its carbohydrate composition and was capable of manufacture in quantities large enough to provide effective treatment.

With this understanding of the technology, it is clear that claims 2 and 4 of the '080 patent, by themselves, do not define "therapeutically effective" beyond its plain and ordinary meaning, nor do they indicate that a "therapeutically effective amount" of EPO is one that does more than elicit the biological effects noted in claim 2. Instead, claim 2 stakes out Amgen's novel recombinant EPO that has the same in vivo biological activities of natural EPO (causing bone marrow cells to increase production of reticulocytes and red blood cells). Claim 4 sets out a pharmaceutical composition that has a novel amount of the EPO—an amount that can actually treat or cure patients. Notably, these claims do not indicate whether biological effects are themselves sufficient to treat or cure patients.

Similarly, the claims of the '422 patent do not define a "therapeutically effective amount" as one that does something above and beyond eliciting the biological effects of EPO listed in the specification.

The next question is whether the claims themselves indicate for what types of patients this product is "therapeutically

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Mem. in Opp'n re '422/'080 at 19. While the expert testimony does support the plain and ordinary meaning of the term since it defines what "cure" means in the context of anemia patients, the Court will not rely on it to construe the claim, because even the *Altiris* court made clear that it was looking to expert testimony merely to understand the technology—not to construe the term itself.

effective." Amgen contends that its EPO is specifically designed for those suffering from anemias and thus only an increase in hematocrit is "therapeutically effective." Indeed, the record shows that Amgen's product *can* be used to increase levels of hematocrit, in other words, it *can* be used to "cure" or "relieve" the diseased state brought on by anemia. *Amgen I*, 126 F. Supp. 2d at 99 ("The therapeutic effectiveness or benefit of an erythropoietin preparation is shown by demonstrating a correction in anemia by increasing and maintaining the hematocrit of a patient to normal or near normal levels.").[28] Dr. Erslev testified at the first trial that a sustained increase in hematocrit and hemoglobin is required to determine whether or not anemia has been corrected. Erslev Test., Trial Tr. at 1688: 14- 1689: 4; Means Test., Trial Tr. at 1905: 17-20; 1910: 9-13. Dr. Erslev also testified that the other effects listed in the specification such as an increase in reticulocyte count or an increase in iron uptake cannot—each standing alone—correct anemia. Erslev Test., Trial Tr. at 1688: 14-1689: 4.

The problem with Amgen's argument, however, is that the claims that contain the disputed term do not themselves include a limitation directed to the specific clinical benefit of correcting *anemia*. Therefore, the plain and ordinary meaning of "therapeutically effective" cannot be limited to curing *anemia*, i.e., producing an increase in hematocrit levels based on the claims alone. The claim language simply does not allow for such a specific interpretation. This conclusion is further supported by the fact that claim 6 of the '080 patent (unlike claim 4) does indeed specify the type of treatment

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[28] While the Court cannot rely on expert testimony to help construe the term "therapeutically effective" unless absolutely necessary, it may look to the expert testimony to better understand the technology. *Vitronics*, 90 F.3d at 1584; *Altiris*, 318 F.3d at 1371. In this respect, the expert testimony that Amgen offers helps the Court understand what is necessary in order to "cure" the effects of anemia.

(kidney dialysis) for which the EPO should be used and calls out, in that context, that an effective amount is one that increases hematocrit:

> *'080 Claim 6*: A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 4 in an amount effective to increase the hematocrit level of said patient.

'080 Patent, Ex. 1, col. 38: 57-60. Had Amgen used similar claim language in claim 4—that is, had it referred specifically to anemia—then its argument would have merit. Based on the nonspecific language of claim 4, however, this argument fails.

In sum, the claim language supports only the plain and ordinary definition of "therapeutically effective"—an amount that produces a result that, in and of itself, helps to heal or cure. The language of the claims at issue does not delineate the type of disease for which the EPO is "therapeutically effective." Therefore, the Court must now turn to the specification and the prosecution history to determine whether Amgen has limited or altered the plain meaning of the term either by defining the term or specifying the disease states for which the product is intended.

c. The Specification

The second step in claim construction is to review the specification to determine whether the patentee has used terms in a manner inconsistent with the ordinary meaning or has become his own lexicographer. *Vitronics*, 90 F.3d at 1582. In essence, "[t]he specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Id.* (noting that the specification is "the single best guide to the meaning of a disputed term"). The Federal Circuit has stated that "a claim must be read in view of the specification of which it is part," and therefore, a court can use the written description to define a

term that is already in a claim limitation. *Renishaw*, 158 F. 3d at 1248; *SciMed Life Sys.*, v. *Advanced Cardiovascular Sys.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) (noting that claims can be given a narrow construction in light of the written description and explaining that one reason to look to the specification is "to determine if the patentee has limited the scope of the claims" (quoting *Watts* v. *XL Systems, Inc.*, 232 F.3d 877, 882 (Fed. Cir. 2000))).

The part of the specification to which the Federal Circuit in *Agmen II* pointed is as follows:

> Similarly, *to the extent* that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects *herefore* attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis *(see, Eschbach, et al., supra) and,* as indicated in Example 10, increasing hematocrit levels in mammals.

'933 Patent, Ex. 1, col. 33: 19-31 (emphases added).

The Court begins by analyzing whether this section defines therapeutically effective to include the effects listed above. It is undisputed that this section declares that Amgen's recombinant EPO is similar to natural EPO in that it shares some of the same in vivo activity. *Id.* at col. 33: 19-22. "*[T]o the extent*" that it does so—to the extent that it is similar to natural EPO—Amgen's EPO are "conspicuously suitable for use in erythropoeitin therapy procedures" to develop any or all of the effects that were "herefore" (before) attributed in vivo to EPO, such as the stimulation of reticulocyte response, development of ferrokinectic effects, erythrocyte

mass changes, and stimulation of hemoglobin C synthesis. What is unclear and disputed, however, is whether the section that begins with "and, as indicated in Example 10, increasing hematocrit levels in mammals" is part of the laundry list of effects previously attributed in vivo to EPO or a separate suitable use for the product. In other words, this portion of the specification can be interpreted one of the following two ways:

> 1) Amgen's EPO is "conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, . . . and, as indicated in Example 10, increasing hematocrit levels in mammals."
>
> 2) Amgen's EPO is "conspicuously suitable for" (a) "use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, . . ." *and*, (b) "as indicated in Example 10, increasing hematocrit levels in mammals."

The former interpretation—a direct quote of the specification—suggests that an increase in hematocrit level was an effect previously attributed to natural EPO and that it, along with the biological effects, are a type of effective therapy. In other words, it includes "increasing the hematocrit levels" as *one of the many effects* of EPO that were previously identified and that are now produced by this product and useful in "erythropoietin *therapy* procedures." The problem with this reading is that the intrinsic evidence (the claims, the specification, and the prosecution history) and extrinsic evidence suggest that an increase in hematocrit levels was *not* previously attributed to natural EPO.[29] In remarks following

[29] Again, extrinsic evidence is being used to understand the technology—not to define the term.

an amendment made during prosecution of the '080 patent, Amgen explained to the Patent and Trademark Office ("PTO") that Example 10 is novel in that it is the first therapeutic procedure ever practiced with EPO to demonstrate that EPO has the capacity to generate an increase in hematocrit in vivo. Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 179. The extrinsic record also suggests that an increase in hematocrit was not previously attributed to natural EPO. *Vitronics*, 90 F.3d at 1583 ("Included within an analysis of the file history may be an examination of the prior art cited therein."). Therefore, the first reading implies a factually incorrect conclusion.

The latter interpretation—and the one that the Court adopts—suggests that an increase in hematocrit is independent or different from the in vivo effects previously attributed to natural EPO. In other words, in this section, Amgen calls out that its recombinant EPO can elicit "any or all" of the effects that natural EPO does—and more. Admittedly, the use of the words "therapy procedures" supports the interpretation that a "therapeutically effective amount" encompasses an amount that would result in the biological effects because it implies that the effects are a part of therapy. That being said, however, the way in which the increase in hematocrit is set off from the rest of the language suggests that this product elicits something in addition to what the prior art elicited, something more than the biological effects. Moreover, it makes clear that "any or all" only modifies those effects previously attributed to natural EPO—not the increase in hematocrit. Indeed, if the phrase "as indicated in Example 10, increasing hematocrit levels in mammals" were merely an item in the list of "any or all of the effects herefore attributed in vivo to EPO," then the words "in mammals" would be redundant. The list of items refers to "effects herefore attributed in vivo to EPO" for "use in erythropoietin therapy procedures practiced *on mammals*", so "increasing hematocrit

levels *in mammals*" must be a second end for which Amgen's EPO is "conspicuously suitable."

This interpretation comports with the Court's understanding—developed over the course of two intensive trials—of what hematocrit actually measures. Hematocrit measures the ability of the blood to supply oxygen to the body. It indicates the relative proportion of red blood cells to the total volume of blood. By introducing additional EPO into the patient's body, a patient's hematocrit level can be increased to and sustained at or near normal levels. In other words, the blood is able to provide a steady supply of sufficient oxygen to the tissues. It is the Court's understanding that, in *most* cases, an increase in hematocrit is accompanied, if not preceded, by "any or all" of the biological effects listed in the specification.[30] In other words, this portion of the specification explains what happens when a "therapeutically effective amount" of EPO is used—that is, it produces an increase in hematocrit—along with any or all of the biological affects previously attributed to natural EPO. As will be discussed below, this reading is further supported by other parts of the specification and the prosecution history.

Therefore, while this Court agrees with the Federal Circuit that therapeutic effectiveness "encompasses the patient responses described in the specification," this part of the specification does not indicate that these biological responses are sufficient or that Amgen "broadened" the plain meaning

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[30] This is consistent with HMR/TKT's argument with respect to validity and Goldwasser that the biological effects are critical steps in the development of red blood cells, HMR/TKT's Proposed Findings of Fact after Trial [Doc. No. 807] ¶¶ 64-66, and expert testimony. Experts on both sides agree that the biological effects are surrogate markers or early indicators that a therapeutic effect will follow. Foster Test., R. Trial Tr. at 946-47, 965; Schumacher Test., R. Trial Tr. at 807: 3-5, 813: 3-18; Eschbach Test., R. Trial Tr. at 660: 22 to 661: 8, 669: 10-670: 2, 766: 4-17; Christensen Test., R. Trial Tr. at 1185: 1-17, 1186: 9-24.

of the term "therapeutically effective" to encompass the elicitation of biological effects alone regardless of whether they heal or cure. Indeed, the term "therapeutically effective" is never even mentioned in this section of the specification. While guidance as to a claim term's meaning or a claim's scope need not be provided in explicit definitional format, *SciMed Life Systems*, 242 F.3d at 1344, to alter the plain and customary meaning of a term that is not ambiguous on its face, a patentee must do so clearly and deliberately. *Renishaw*, 158 F.3d at 1249 (noting that when a patent applicant "has elected to be a lexicographer by providing an explicit definition in the specification for a claim term[,] . . . the definition selected by the patent applicant controls" as long as the patentee's lexicography is made "'with reasonable clarity, deliberateness, and precision'" (quoting *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994))); *Vitronics*, 90 F.3d at 1582; *Altiris*, 318 F.3d at 1370.[31] Here, there is no "manifest exclusion or restriction, representing a clear disavowal of claim scope." *Teleflex, Inc.* v. *Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002). Thus, this portion of the specification does not redefine the plain and ordinary meaning of the term to include the biological effects regardless of whether they heal or cure. Likewise, this portion of the specification does not limit the term to an increase in hematocrit. While it makes clear that its product is useful

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[31] This is not to suggest that the specification cannot provide guidance as to the scope of the claims absent a clear and deliberate act of lexicography by the patentee. Indeed, if the claim's scope cannot be ascertained from the ordinary and plain meaning of the words alone, the specification can assist and even limit the interpretation of the claims. *Teleflex, Inc.* v. *Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002). The relevant portion of the specification, however, does not indicate that the patentee deliberately altered the meaning of "therapeutically effective," and indeed the term at issue is not ambiguous. As will be discussed below, what is ambiguous is for whom the invention is intended to be "therapeutically effective."

because it can increase hematocrit, it does not redefine the term in question to equate only with an increase in hematocrit (or relate only to curing anemia).

Amgen points to a few other portions of the specification in support of its argument that while it did not alter the meaning of "therapeutically effective" to include the biological effects, it did limit the claimed therapy to patients suffering from anemia and anemia-like disorders and likewise limited the claim to an increase in hematocrit.[32]

The first such passage is the one immediately following the portion of the specification cited by the Federal Circuit:

> *Included within* the class of humans treatable with products of the invention are patients generally requiring blood transfusion and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

'933 Patent, Ex. 1, col. 33: 31-36 (emphasis added).[33] As HMR/TKT correctly points out, this list of patients is obviously incomplete as it begins with the words "included within," which suggests that there are other types of patients for which the product is intended. HMR/TKT's Post-Hr'g Mem. [Doc. No. 747] at 4. While this is true, it still provides insight into the type of patients who may receive a therapeutic benefit from the pharmaceutical compositions of the invention. Therefore, while the specification does not actively limit

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[32] If Amgen limited the invention to patients suffering from anemia, then by default the definition of "therapeutically effective" equates with an increase in hematocrit *if* only an increase in hematocrit heals or cures anemia.

[33] All of these patients are in many respects transfusion-dependent. Extrinsic evidence demonstrates that it is an increase in hematocrit which eliminates the need for transfusions.

the term to this class of patients, it provides guidance to the Court in defining the term. *Vitronics*, 90 F.3d at 1582; *Teleflex, Inc.*, 299 F.3d at 1325 ("The specification may assist in resolving ambiguity where the ordinary and customary meaning of the words used in the claims lack sufficient clarity to permit the scope of the claim to be ascertained from the words alone."). By listing the types of patients responding to treatment by the product, the specification implies that the term "therapeutically effective" amount was written with respect to these types or classes of patients. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by *implication*." *Vitronics*, 90 F.3d at 1582 (emphasis added).[34] It does not, however, indicate that this invention is only for the treatment of anemia but instead for all the ailments listed. While this may not be an exhaustive list and patients with similar or like disorders might also benefit from the product, this list begins to infuse "therapeutically effective amount" with real meaning.

Other portions of the specification support interpreting the claims with reference to the class of patients listed in the specification. For example, the specification states: "The minimization of the need for transfusion therapy through use of EPO therapy can be expected to result in reduced transmission of infectious agents." '933 Patent, Ex. 1., col. 33: 37-39. While this is only one example of how the product

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[34] If this were not the case, arguably, the patent would be invalid for indefiniteness. Issued patents are presumed to be valid, 35 U.S.C. § 282; *National Recovery Techs., Inc.* v. *Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999), and "claims should be construed to sustain their validity," *Rhine* v. *Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999); *see also Amgen I*, 126 F. Supp. 2d at 83. The Court need not address, however, whether the likelihood that a broad construction would render the '933 patent invalid is significant enough to provide an alternative justification for the narrower construction on which the Court has settled.

is useful or advantageous, it falls within the class of patients listed in the specification.[35]

Other pertinent sections are as follows:

> It has recently been estimated that the availability of erythropoietin in quantity would allow for treatment each year of anemias of 1,600,000 persons in the United States alone.

Id. at col. 6: 35-39.

> . . . clinical testing and potential wide-ranging *therapeutic use* of [Lin's recombinant EPO] in treatment of e.g., chronic kidney disease wherein diseased tissues fail to sustain production of erythropoietin.

Id. at col. 9: 6-9 (emphasis added).

> *Also* comprehended by the invention are pharmaceutical compositions comprising effective amounts of polypeptide products of the invention together with suitable diluents, adjuvants and/or carriers which allow for provision of erythropoietin therapy, *especially in* the treatment of anemic disease states and most especially such anemic states as attend chronic renal failure.

Id. at col. 12: 1-7 (emphasis added).

> Because erythropoietin is essential in the process of red blood cell formation, the hormone has potential useful

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[35] Amgen argues that the "minimization of the need for transfusion therapy"—which is used to increase the oxygen transport capacity of the blood—can only be achieved by raising an anemic patient's hematocrit for a sustained period. Amgen's Mem. in Support re '422/'080 at 12. Therefore, it argues that this section supports its contention that the term "therapeutically effective" means an increase in hematocrit. *Id.* This section, however, is merely explicating one example of how the product is useful or advantageous—just as the section on the class of patients included patients suffering from anemias that can be cured by an increase in hematocrit but also included patients in need of blood transfusions.

> application in both the diagnosis and the *treatment* of blood disorders characterized by low or defective red blood cell production.

Id. at col. 6: 20-24 (emphasis added).[36]

Amgen also points to column 6, lines 28-33 of the '933 patent, which cites a study done by Eschbach:

> *See*, generally, . . . Eschbach, et al[.] . . . describing a therapeutic regimen for uremic sheep based on in vivo response to erythropoietin-rich plasma infusions and proposing a dosage of 10 U EPO/kg per day for 15-40 days as corrective of anemia of the type associated with chronic renal failure.

That Amgen intended its invention to treat anemic patients is clear from these sections (along with the prosecution history, as will be discussed below) and is pertinent to the analysis. *Renishaw*, 158 F.3d at 1250 (noting that what the "inventors actually invented and intended to envelop with the claim" is relevant in claim construction); *CVI/Beta Ventures* v. *Tura LP*, 112 F.3d 1146, 1160 (Fed. Cir. 1997) ("In construing claims, the problem the inventor was attempting to solve, as discerned from the specification and the prosecution history, is a relevant consideration."). None of these sections, however, shows that Amgen intentionally re-defined the plain meaning of the term "therapeutically effective" to refer exclusively to anemia or to an increase in hematocrit.

While these sections do not suggest that the product is solely intended for anemic patients and to increase hematocrit, they do imply, in combination, that it is designed for

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[36] As will be discussed *infra*, the extrinsic evidence shows that an increase in hematocrit is necessary to cure defective red blood cell production effectively.

the class of patients listed in column 33 and noted above.[37] That being said, it seems to stretch the doctrine of claim construction too far to incorporate into the plain and ordinary meaning a reference to a class of patients that at best is only implied in the specification. *Northern Telecom Ltd.* v. *Samsung Elecs. Co.*, 215 F.3d 1281, 1294 (Fed. Cir. 2000); *KX Indus., L.P.* v. *PUR Water Purification Prods.*, 18 Fed. Appx. 871, 876 (Fed. Cir. Aug. 10, 2001) (unpublished opinion)[38] ("[W]hat is determinative is whether the patentee has defined a claim term as excluding a broader interpretation with reasonable clarity and deliberateness."). On the other hand, it seems foolish to construe a term such as "therapeutically effective," without reference to a class of patients for which the product is intended to be "therapeutically effective." This quandary, however, is put to rest by the prosecution history. When the specification is considered along with the prosecution history, it becomes apparent that a class-of-patients limitation is appropriate.

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[37] As will be discussed at great length *infra*, if the term "therapeutically effective" is properly construed only with reference to this class of patients, it is irrelevant whether Amgen actually refined the term to mean an "increase in hematocrit" as the evidence at trial confirmed that these types of patients are only healed or cured by an increase in hematocrit and not by any of the biological effects.

[38] Citing an unpublished opinion raises a number of difficult questions. *See Anastasoff* v. *United States*, 223 F.3d 898, 899-905 (8th Cir. 2000) (Arnold, J.) (holding that unpublished opinions have precedential effect), *vacated as moot*, 235 F.3d 1054 (8th Cir. 2000) (en banc), *Giese* v. *Pierce Chem. Co.*, 43 F. Supp. 2d 98, 103 n.1 (D. Mass. 1999) (relying on unpublished opinions' persuasive authority); Hon. Richard S. Arnold, *Unpublished Opinions: A Comment*, 1 J. App. Prac. & Process 219 (1999); *see also* Proposed Fed. R. App. P. 32.1; Anne Coyle, Note, *A Modest Reform: The New Rule 32.1 Permitting Citation to Unpublished Opinions in the Federal Courts of Appeals*, 72 Ford. L. Rev. 2471 (2004). *But see* Hon. Alex Kozinski, Letter, Fed. Law., June 2004, at 37.

d. The Prosecution History

The third step in claim construction is to consider the prosecution history to determine whether the applicant has made any express representations regarding the claim's scope. *Vitronics*, 90 F.3d at 1582-83; *Standard Oil Co.* v. *American Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985) ("[A]ll express representations made by or on behalf of the applicant to the examiner to induce a patent grant . . . [can] limit[] the interpretation of claims."); *Alpex Computer Corp.* v. *Nintendo Co. Ltd.*, 102 F.3d 1214, 1220 (Fed. Cir. 1996) (noting that prosecution history is "relevant . . . for construing the meaning and scope of the claims").

The amendments made early on in pursuance of the patents support HMR/TKT's contention that Amgen defined a "therapeutically effective amount" of EPO to encompass an amount sufficient to elicit any or all of the biological effects that were attributed to natural EPO.

On December 5, 1988, in response to a rejection under 35 U.S.C. §§ 112, 102(b) and 103 of what eventually became the '080 patent, Amgen submitted independent claim 41 and dependent claims 55-57 and 61-66. The pertinent amendments are claim 41 (which relates to claim 2 of the '080 patent), claim 55 (which relates to claim 4 of the '080 patent), claim 57 (which relates to claim 6 of the '080 patent), and claim 56 (because it is referenced in claim 57).

> *Claim 41:* A glycoprotein product having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

> *Claim 55:* A pharmaceutical composition comprising an effective amount of a glycoprotein product according to claim 41 and a pharmaceutically acceptable diluent, adjuvant or carrier.
>
> *Claim 56:* A method for providing erythropoietin therapy to a mammal comprising administering an effective amount of a glycoprotein product according to claim 41.
>
> *Claim 57:* A method according to claim 56 wherein the therapy comprises enhancing hematocrit levels.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 174-75.

These claims make clear that Amgen's product purposefully duplicates natural EPO in that it elicits the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, but that it differs from natural EPO in its carbohydrate composition. These claims also make clear that claim 55 (similar to claim 4 in the '080 patent) is not limited to increasing hematocrit because that is precisely what claim 57 does (and what claim 6 in the '080 patent now does). In the remarks accompanying the amendment, Amgen twice explained that its product produces the same in vivo biological activity as that of natural EPO:

> Applicant's novel glycoprotein preparations . . . hav[e] the glycosylation-requiring *in vivo* biological activity (promoting reticulocyte and red blood cell production) characteristics of naturally occurring human erythropoietin.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 175.

> [T]he glycoprotein products herein claimed . . . possess the essential *in vivo* biological activity of naturally occurring erythropoietin.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 181. It then explained, with reference to claim 56, that Amgen "first

developed knowledge of the full amino acid sequence of erythropoietin and first generated the presently claimed glycoprotien products which allowed for full scale clinical application to provide *therapeutic effects* consistent with the *in vivo* activity of naturally occurring erythropoietin." *Id.* at 177 (first emphasis added). With reference to claim 41, it stated that Amgen "was the first to provide a glycoprotein which is *both* different from previously isolated urinary erythropoietin in its glycoyslation and yet sufficiently like the natural product . . . in terms of its glycosylation to allow it to fill the long-felt need (unsatisfiable by urinary isolates) for life-sustaining human therapeutic agents for, e.g., the anemia associated with dialysis in renal failure patients." *Id.* at 178. It then explained that the product is "sufficiently like" natural EPO in glycosylation because it "allow[s] for *in vivo* biological activity." *Id.* at 179. Later, it explained that Example 10 is novel in that it is the first therapeutic procedure ever practiced with EPO to demonstrate that EPO has the capacity to generate in vivo an increase in hematocrit. *Id.*

Taken in combination, the amendments and these remarks support the interpretation that Amgen intended "therapeutically effective amounts" of EPO to encompass an amount that elicited in patients any or all of the biological effects previously attributed to natural EPO and that it did not limit the term to an increase in hematocrit.[39] Such an effect is separately claimed in claim 6 (here claim 57).

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[39] The specification at that time confirms this interpretation:

> Novel glycoprotein products of the invention includes those having a primary structural conformation sufficiently duplicative of that of a naturally-occurring (e.g., human) erythropoietin to allow possession of one or more of the biological properties thereof and having an average carbohydrate composition which differs from that of naturally-occurring (e.g., human) erythropoietin.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 180; *see also id.* at 181.

Were this the entire prosecution history, the Court would agree with HMR/TKT and the Federal Circuit that Amgen broadened the term to mean one that elicits any or all of the in vivo effects before attributed to natural EPO regardless of whether they actually heal or cure the patient. In the course of overcoming two additional rejections later on in the process, however, Amgen differentiated its product from natural EPO (i.e., it overcame rejection) by asserting that natural EPO—which elicits the biological effects—was not therapeutically viable, whereas its product was clinically effective and designed specifically for a class of patients for which the product was intended. In doing so, Amgen avowed that its invention produced enough quantity of EPO to elicit responses that actually healed or cured the patient. *Renishaw*, 158 F.3d at 1249 n.3 ("[A]ny interpretation that is provided or disavowed in the prosecution history also shapes the claim scope."); *Standard Oil Co.*, 774 F.2d at 452 ("[T]he prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.").

For example, in a June 5, 1989 amendment, in response to a PTO rejection under 35 U.S.C. § 103 for obviousness, Amgen distinguished its recombinant EPO product from natural EPO by claiming natural EPO was "not a viable therapeutic product" whereas its recombinant EPO was "clinically effective" and the "first therapeutic product" successfully to treat anemia and other disorders involving low red blood cell counts:

> All of the references cited by the Examiner in this rejection relate to naturally occurring erythropoietin. The claims of the subject invention relate to erythropoeitin which is produced through recombinant DNA techniques. Recombinant erythropoietin is different from naturally occurring erythropoietin. . . Moreover, natur-

> ally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proven to be clinically effective, *and* is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 11, at 227 (emphasis omitted). Amgen further explained that "[i]n contrast to recombinant erythropoietin, naturally occurring human erythropoietin is not used to treat patients. In the past, efforts were made to obtain purified erythropoietin from natural sources . . . . The results of these efforts however yielded only a small amount of material which was far too little for clinical research." *Id.* at 229. As the FDA stated in its approval of recombinant EPO "there is not enough naturally occurring enthropoetin produced to collect it from healthy persons for use in treatment," but "gene splicing techniques have permitted its production." *Id.* Thus, in response to this rejection, Amgen differentiated its EPO from natural EPO in two respects. First, Amgen claimed its invention allowed for a sufficient amount of EPO actually to treat patients—as opposed to natural EPO which was not available in large enough quantities. Second, it claimed its EPO, as opposed to prior art, effectively treated patients suffering from anemia or other disorders involving low red blood cell count.[40] This was a clear and definitive statement about what the invention "envelopes." *Renishaw*, 158 F.3d at 1250 (noting that a term can only be properly interpreted "with a full understanding of what the inventors actually

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[40] This supports Amgen's contention that it defined "therapeutically effective" as an increase in hematocrit since, as will be discussed *infra*, the evidence shows that an increase in hematocrit—unlike the other biological effects listed in the specification—cures or heals the diseased states mentioned in the specification.

invented and intended to envelop with the claim" and that the correct construction is that which "stays true to the claim language and most naturally aligns with the patent's description of the invention"). Here, the prosecution history makes clear that Amgen intended its invention to be clinically effective at least for the class of patients suffering from anemia and low red blood cell disorders. *See Standard Oil Co.*, 774 F.2d at 452 ("[A]ll express representations made by or on behalf of the applicant to the examiner to induce a patent grant or . . . to reissue a patent . . . [can] limit[] the interpretation of claims."); *Spectrum Int'l Inc.* v. *Sterilite Corp.*, 164 F.3d 1372, 1378 (Fed. Cir. 1998) ("[E]xplicit statements made by a patent applicant during prosecution to distinguish a claimed invention over prior art may serve to narrow the scope of the claim."). Amgen was trying to cure anemia and other diseases associated with low red blood cell count—not simply to duplicate the effects of natural EPO regardless of whether those effects cured or healed. *CVI/Beta Ventures*, 112 F.3d at 1160 ("In construing claims, the problem the inventor was attempting to solve, as discerned from the specification and the prosecution history, is a relevant consideration.").

That Amgen intended its invention to provide a meaningful health benefit to the list of patients expressly mentioned in the specification is supported by another portion of the prosecution history. On November 6, 1990, Amgen claimed the following in an application that eventually resulted in the '422 patent:

> *Claim 61:* An erythropoietin-containing, pharmaceutically-acceptable composition wherein human serum albumin is mixed with erythropoietin.
>
> *Claim 62:* A composition according to claim 61 containing a therapeutically effective amount of erythropoietin.

> *Claim 63:* A composition according to claim 61 containing a therapeutically effective amount of recombinant erythropoietin.[41]

HMR/TKT's App. to Opp'n [Doc. No. 705], Tab 2 (Ex. 2003, 11/6/90 Preliminary Amendment) at 9. The examiner rejected claims 62 and 63 as "being indefinite for failing to particularly point out and distinctly claim the subject matter which [the] applicant regard[ed] as the invention." *Id.* (Ex. 2003, 6/1/94 Examiner's Action) at 2. Claim 62 was rejected for being "vague and indefinite because it is unclear what the claimed composition is required to be 'effective' for," and claim 63 was rejected as "vague and indefinite because it is unclear as to how the recitation that the claimed erythropoietin is 'recombinant' modifies the physical erythropoietin composition[;] . . . while the claimed erythropoietin may be prepared using recombinant techniques, the product would not necessarily distinguish over that found in nature." *Id.* In essence, then, the examiner rejected Amgen's patent because it did not specify for what type of patients the product was intended to be "therapeutically effective" *and* it did not distinguish how the recombinant EPO was different than natural EPO besides its preparation. In other words, it did not differentiate what recombinant EPO provided to patients that natural EPO did not.

Amgen requested reconsideration, stating that the terms "effective" and "recombinant" are, "in view of the extensive disclosure of the specification," well-defined and understood by a person of skilled in the art. *Id.* (Ex. 2003, 12/1/94 Request for Reconsideration) at 1. Amgen argued that "the specification indicates *several potential therapeutic uses* for the claimed invention." *Id.* at 2 (emphasis added). It then

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[41] These were the original claim numbers in the application 08/100,197 for what is now the '422 patent. Also, the word "composition" was crossed out and handwritten above it was the word "preparation."

quoted the exact portion of the specification to which the Federal Circuit had pointed, where the in vivo effects along with the effect of an increase in hematocrit levels are mentioned. *Id.* Importantly, however, Amgen also quoted the following sections regarding the class of humans treatable with products:

> Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects heretofore attributed in vivo to EPO e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (*see, Eschbach, et al*[.], *supra*) and[,] as indicated in Example 10, increasing hematocrit levels in mammals. Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias[,] and the like.

Id. (Ex. 2003, 12/1/94 Request for Reconsideration) at 2 (emphasis omitted) (quoting '933 Patent, Ex. 1, col. 33: 19-36). According to Amgen,

> these sentences from the specification and others provide a clear and definite description of the *uses for which the claimed erythropoietin compositions would be therapeutically effective*. A person of skill in the art would understand that the amount of erythropoeitin necessary to achieve these defined therapeutic results would vary for each use. However, *clinicians can readily determine*

> *the "therapeutically effective" amounts for each condition, and indeed for each patient.*

Id. (emphasis added).

The question then is what are the "uses" to which Amgen refers. At first blush, it may appear that the "therapeutic uses" are the effects listed in the specification. A close reading of the remarks, however, makes clear that the words "uses" and "use" refer to treatment of the conditions listed in the specification—not to eliciting the effects. If this were not the case, the following sentence would not make sense: "A person of skill in the art would understand that the amount of erythropoeitin necessary to achieve these defined therapeutic results would vary for each *use*." *Id.* (emphasis added). Amgen overcame a rejection of indefiniteness, in part by claiming that its product was specifically designed to treat patients suffering from the types of disease listed in the specification. Such a clear avowal—when considered alone or along with the other parts of the prosecution history and specification—would estop Amgen now were it to try to claim that its product was "therapeutically effective" in treating patients with *high* red blood cell counts. *Alpex Computer Corp.*, 102 F.3d at 1221 ("Just as prosecution history estoppel may act to estop an equivalence argument under the doctrine of equivalents, positions taken before the PTO may bar an inconsistent position on claim construction."); *Ekchian* v. *Home Depot, Inc.*, 104 F.3d 1299, 1304 (Fed. Cir. 1997) ("[B]y distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover, [and] he is by implication surrendering such protection."). Here we have prosecution history estoppel in reverse—that is, Amgen wants this Court to constrain the meaning of the term to this class of patients. This does not change the effect the Court must give Amgen's clear and definite statements. Thus, the Court holds that Amgen limited the term in dispute to refer to the class of

patients listed in the specification and quoted to the examiner. *Telefex*, 299 F.3d at 1327 (noting that a term can be limited or extended by the specification or prosecution history as long as the patentee *clearly* intended to do so); *Altiris*, 318 F.3d at 1370 (same).[42]

The trickier question, however, is whether these remarks define the disputed term to include the in vivo effects of EPO *regardless* of whether they heal or cure this class of patients.[43] While it is a close call, the Court does not so read these remarks. Admittedly, all of the effects—the in vivo effects and an increase in hematocrit—are labeled together as "therapeutic results." What is not made clear, however, is whether "therapeutic results" equates with "therapeutically effective." While there is support for reading the terms as coextensive, there is also support for viewing them differently. Amgen specifically differentiates between an amount that achieves therapeutic *results* and a "therapeutically effective amount:"

> A person of skill in the art would understand that the *amount* of erythropoeitin necessary to achieve these defined therapeutic results would vary for each use. However, clinicians can readily determine the *"thera-*

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[42] While "it is improper for a court to add extraneous limitations to a claim," *Hoganas AG* v. *Dresser Indus., Inc.*, 9 F.3d 948, 950 (Fed. Cir. 1993), this limitation, as explained earlier, is not "extraneous." Without a limitation regarding the class of patients to which recombinant EPO is useful, it is impossible to "interpret what the patentee meant" by the disputed term.

[43] As with the specification, these remarks make clear that any or all of the biological effects are part and parcel of therapeutic effectiveness, that is, that Amgen refined "therapeutically effective amount" to be one that, at the least, elicits one or more of the in vivo effects heretofore attributed to natural EPO.

> *peutically effective"* amounts for each condition, and indeed for each patient.

HMR/TKT's App. to Opp'n, Tab 2 (Ex. 2003, 12/1/94 Request for Reconsideration), at 2 (emphasis added). These two sentences indicate that a different amount of EPO is used to achieve each of the effects listed in the specification—including the in vivo effects—depending on the condition and needs of the patient, *but* that a clinician can determine the amount that would be "therapeutically effective." Thus, when read together, these sentences indicate that (1) the biological effects listed in the specification are part of the "therapy" but not necessarily "therapeutically effective," i.e., they do not necessarily heal or cure the patient, and (2) the amount necessary for therapeutic effectiveness—an amount that heals or cures—depends on the types of patients to which the recombinant EPO is being administered.

Because these remarks do not clearly disavow the ordinary and customary meaning of the disputed term and can actually be interpreted to support the ordinary and customary meaning of the disputed term,[44] the Court does not construe "therapeutically effective" to encompass any or all of the biological effects regardless of whether they work to heal or cure. *Amgen II*, 314 F.3d at 1327 ("We indulge a heavy presumption that a claim term carries its ordinary and customary meaning . . . [P]rosecution history may not be used to infer the intentional narrowing of a claim absent the applicant's clear disavowal of claim coverage."); *see KX Industries, L.P.* v. *PUR Water Purification Prod.*, 18 Fed. Appx. 871, 876 (Fed. Cir. 2001) (unpublished opinion); *see also Northern*

[44] Although the Court does not read them as such, these sentences *could* be interpreted to support that "therapeutically effective" includes the biological effects. This ambiguity, however, does not establish HMR/TKT's point. To the contrary, it demonstrates that the patentee did not clearly and deliberately redefine the term and that the plain and ordinary meaning should prevail.

Telecom Ltd. v. *Samsung Elec. Co.*, Ltd, 215 F.3d 1281, 1294-95 (Fed. Cir. 2000) (analyzing whether the patentee in the prosecution history "with reasonable clarity and deliberateness" excluded a broader interpretation of the claims).[45] In further support of this conclusion is the fact that the examiner allowed the claims to stand. As the Federal Circuit pointed out in a slightly different context in *Amgen II*, "[w]e must presume the examiner did his job, and if he truly thought that" Amgen's EPO was the same as natural EPO in that it merely elicited the biological effects, "the asserted claims would not have issued." 314 F.3d at 1327.[46]

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[45] This ambiguity itself is helpful to Amgen, given that "claims should be construed to sustain their validity" and Amgen is not advancing a definition of the term that is contrary to the plain and ordinary meaning. *Rhine* v. *Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999); *see also Amgen I*, 126 F. Supp. 2d at 83 ("[T]he canon that claims terms ought be construed to sustain their validity is simply an interpretation tool to aid courts in determining what a reasonably disputed claim term means in light of the specifications."). If the Court were to construe the term as HMR/TKT urges—as covering mere biological responses—the claims would likely be invalid as anticipated by prior art.

[46] Further support for the conclusion that Amgen was not redefining therapeutic effectiveness to include the biological effects regardless of whether they worked to heal or cure the patient is found in the prior art disclosed to the patent examiner. *Autorigo Co. of America* v. *United States*, 384 F.2d 391, 399 (Fed. Cir. 1967) ("In its broader use as source material, the prior art cited in the file wrapper gives clues as to what the claims do not cover."). Although it appears Amgen did not cite the Goldwasser study, it did disclose it to the examiner. *Amgen I*, 126 F. Supp. 2d at 138-39. As will be discussed *infra*, Dr. Goldwasser obtained a preparation of highly purified EPO derived from human urine. *Amgen I*, 126 F. Supp. 2d at 111-112. He administered EPO to three anemic patients and reported an increase in reticulocyte count in all three patients, an increase in erythroid cells in marrow and increased plasma iron clearance rate in two patients, and an increase in red cell mass in one patient. *Id.* Dr. Goldwasser admitted that there was no significant change in the hematocrit levels of any of the patients and as such, the trial was a failure. *Id.* The fact that Dr. Goldwasser believed his study to be a failure, that is,

5. Conclusion and Claim Construction of "Therapeutically Effective"

The Federal Circuit has stated that "any interpretation [of a patent claim term] that is provided or disavowed in the prosecution history shapes the claim scope." *Renishaw*, 158 F.3d at 1243 n.3; *see Digital Biometrics, Inc.* v. *Identix, Inc.*, 149 F.3d 1335, 1347 (Fed. Cir. 1998) ("The public has a right to rely on such definitive statements made during prosecution."); *Ekchian*, 104 F.3d at 1303-04 (noting that the courts and the public may rely on an information disclosure statement to interpret a claim). Here, to overcome a patent rejection for indefiniteness, Amgen avowed that its invention was "therapeutically effective" for the class of patients listed in column 33 of the specification. Therefore, the Court rules that "therapeutically effective" must be read with reference to this class of patients despite the fact that the specification uses the words "included within." Amgen did not, however, go so far as to limit the list of patients to those suffering from anemia only or refine the term to mean an increase in hematocrit.[47] Nor did Amgen clearly redefine the term "thera-

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that it did not provide a meaningful health benefit to patients when it achieved the biological effects of EPO but not an increase in hematocrit indicates that Amgen's claims are not merely covering the biological effects.

[47] While the specification and prosecution history support Amgen's contention that it defined "therapeutically effective" to mean an increase in hematocrit, the intrinsic evidence does not show a *clear* and *deliberate* attempt to redefine the term this way. Even were this not the case, and the Court ruled there was a clear and deliberate intent to define "therapeutically effective" as an increase in hematocrit—or for that matter had resorted to extrinsic evidence and ruled that this was how those skilled in the art defined the term—the end result regarding validity of these patents in view of prior art would not be different. As will be discussed further below, the evidence shows that the biologic effects of EPO do not elicit any meaningful health benefit to patients. Therefore, the only thing claimed in the patent that actually does heal or cure is an increase in

peutically effective amount" to mean an amount that induces the effects heretofore attributed to natural EPO regardless of whether they work to heal or cure the patient. To the contrary, Amgen repeatedly states in the prosecution history and in the specification that recombinant EPO's novelty is that it can actually effectively treat, that is heal or cure, patients. While "the inventor's subjective intent as to claim scope, *when unexpressed in the patent documents*, [should not] have any effect," *Vitronics*, 90 F.3d at 1584 (emphasis added), the correct construction is that which "stays true to the claim language and most naturally aligns with the patent's description of the invention," *Renishaw*, 158 F.3d at 1243. Throughout the prosecution history, Amgen repeatedly describes the invention as one that *heals* patients suffering from low red blood cell counts—something that could not be done

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hematocrit. Thus, by default the terms "therapeutically effective" and "increase in hematocrit" become synonymous.

As mentioned earlier, an alternate route would have been to consider extrinsic evidence as to the meaning those skilled in the art would give the disputed term. Indeed, much evidence was presented at the first trial on the subject, the bulk of which supports Amgen's contention that one skilled in the art would equate "therapeutically effective" with an increase in hematocrit when considering anemia. Two crucial witnesses for the defense conceded as much. Dr. Means testified that in the routine practice of medicine as it relates to EPO in treating anemia in patients, "an increase in hematocrit is how one defines a response." Means Test., Trial Tr. at 1910: 9-13. Dr. Erslev agreed that the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit. Erslev Test., Trial Tr. at 1675: 12-23. The only problem with relying on such evidence—other than the Federal Circuit's ruling in *Vitronics* and the concern for public reliance on the record—is that this expert testimony was given in reference to anemic patients specifically and did not take into account the entire list of patients in the specification.

In hindsight, however, it appears that this distinction between anemia and the entire list of patients included in the specification is meaningless, for the evidence shows that only an increase in hematocrit provides a meaningful health benefit to the class of patients listed in the specification.

before. While the prosecution history and specification indicate a clear intent to define "therapeutically effective amount" as one that elicits "one or more" of the in vivo effects of natural EPO, they do not define the in vivo effects as *necessarily* being "therapeutically effective." In other words, they do not define these effects as being "therapeutically effective" regardless of whether they heal or cure. Instead, the plain and ordinary meaning of the term "therapeutically effective amount" was refined to (1) *require* (in addition to healing or curing) an elicitation of one or more of the in vivo effects that was attributed to natural EPO and (2) be read in the context of a certain class of patients. Thus, the Court's claim construction is as follows:

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (*see, Eschbach, et al., supra*) and, as indicated in Example 10, increasing hematocrit levels in mammals.
>
> Therapeutically effective is to be interpreted as being therapeutically effective with respect to the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

See 9/18/03 Pretrial Conference Tr. at 9-11.

As will be discussed further below, in deciding whether the Goldwasser reference anticipates Amgen's patents, this construction leaves the Court with a very fact-intensive task: determining which, if any, of the effects listed in the specification actually heal or cure the class of patients referred to therein.

B. "DNA Encoding"

1. Background

At the close of Amgen's case-in-chief during the first trial, this Court granted HMR/TKT's Fed. R. Civ. P. 52(c) motions for judgment of non-infringement of claims 4-9 of Amgen's '698 process patent. *Amgen I*, 126 F. Supp. 2d at 99-101. On appeal, the Federal Circuit vacated and remanded this Court's rulings regarding infringement of the '698 patent because the Court had compared the accused device to the preferred or commercial embodiments of the patent instead of to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1347.

In the memoranda in support and in opposition to each party's motions regarding infringement of the '698 patent, the parties argued different interpretations of the term "DNA encoding" found in claims 4 and 6 of the '698 patent. Thus, the Court concluded that the term is in dispute and needed to be construed in order properly to determine the issue of literal infringement.[48]

2. The Claims at Issue

Claim 4 of the '698 Patent:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase

[48] Neither party objects to the Court now formally construing the term despite the fact that this issue was not raised during the first trial.

> production of reticulocytes and red blood cells comprising the steps of: (a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to *DNA encoding* the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

'698 Patent, Ex. 1, col. 38: 37-47 (emphasis added) (paragraph structure altered).

> *Claim 6 of the '698 Patent*:
>
> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing under suitable nutrient conditions, vertebrate cells comprising amplified *DNA encoding* the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycoslated erythropoietin polypeptide expressed by said cells.

Id. at col. 38: 50-59 (emphasis added) (paragraph structure altered).

3. Summary of the Parties' Arguments

HMR/TKT's proposed claim construction rests on the argument that the word "encoding" means "producing." HMR/TKT's Mem. in Opp'n re '698 [Doc. No. 700] at 8. HMR/TKT argues that the phrase at issue in Amgen's '698 patent means that the DNA actually produces a glycosylated erythropoietin polypeptide having a 166 amino acid sequence. *Id.* In other words, HMR/TKT argues that section (a) of claims 4 and 6 of the '698 patent should be construed to require the production of an EPO protein with 166 amino

acids. *Id.* at 1; HMR/TKT's Reply re '698 [Doc. No. 725] at 3.

Amgen agrees that the term "mature erythropoietin amino acid sequence of FIG 6" refers to a fully processed EPO glycoprotein having a 166 amino acid sequence. Amgen argues, however, that section (a) of the disputed claims refers to the *DNA* that encodes the fully processed EPO glycoprotein—not to the EPO glycoprotein itself. In other words, Amgen argues that the disputed claims refer to the type of DNA that is involved and describe that DNA as one that has a certain sequence, the genetic code, for the amino acid sequence spanning +1 through +166 of Figure 6. Amgen's Reply re '698 [Doc. No. 731] at 6. Amgen asserts that the proper construction of the claim language is "a DNA sequence that contains the genetic code for the amino acid sequence spanning from position +1 through position +166 of Figure 6." Amgen's Reply re '698 at 6. Amgen contends that a process can contain DNA that encodes the full 166 amino acids but result in an end-product that does not have the full 166 amino acid sequence. Thus, according to Amgen, this portion of the disputed claims refers to a *type* of DNA and to what that DNA *encodes*—not the end-protein that is ultimately *produced.*

4. Discussion

It is true that the Court construed the "mature erythropoietin amino acid sequence of FIG. 6," as stated in both the '080 and '698 patent, to mean a mature (fully realized) erythropoietin having 166 amino acids. *Amgen I*, 126 F. Supp. 2d at 100. HMR/TKT's argument that "DNA encoding . . .[the] amino acid sequence of FIG. 6" means that the DNA actually must produce an EPO with a 166 amino acid sequence, however, stretches this construction too far.

The Court notes that HMR/TKT supports its definition of "encoding" primarily with extrinsic evidence—evidence to

which resort ought be had only "if necessary." *Vitronics*, 90 F.3d at 1583. As will be discussed below, use of extrinsic evidence here is not appropriate in construing these terms because "the patent documents, taken as a whole," are sufficient "to enable the court to construe [the] disputed claim terms." *Id.* Moreover, even if it were necessary, and thus appropriate, for this Court to consider extrinsic evidence as to the meaning of the word "encoding," HMR/TKT's arguments would still fail. HMR/TKT misinterprets the extrinsic evidence to which it points from the first trial. Dr. Kingston did indeed state that "the protein that is encoded is the protein that is actually produced," Kingston Test., Trial Tr. at 1390-91, but this does not define "DNA encoding" as referring directly and exclusively to the specific product that is actually produced. Instead, what this language requires is DNA that is *capable* of encoding the final product—not DNA that produces the final product. HMR/TKT's interpretation of Dr. Lodish's testimony is also faulty. In the trial transcript pages to which HMR/TKT referred, Dr. Lodish never states that "encoding" means "producing," nor does Dr. Lodish define the fragment in question. He does indeed explain the end of the process as one that produces the same EPO glycoprotein. Lodish Test., Trial Tr. at 156-60. But this is the same point. Amgen's argument, and it is a sound one, is that this part of the claim is not describing the last step of the process, but an interim step—one that requires a DNA with a certain type of sequence or encoding capability.

Furthermore, the extrinsic evidence adduced during the second trial shows that "DNA encoding" in these claims does not mean that the end product must be produced. Dr. Lodish testified that those of skill in the art at the time would understand the plain meaning of the disputed term to mean "a DNA which when copied into RNA, and if necessary spliced, specifies the order of amino acids that are the mature erythropoietin amino-acid sequence depicted in Figure 6 of

the patent."[49] Lodish Test., R. Trial Tr. at 1054: 17-22, 1058: 10, 1059: 1-3 (explaining that genes have two parts, one of which involves the "coding sequence, the piece of DNA that actually specifies the amino acids in the encoded product" and stating that it is this part that is the subject of the claim, "that is, it is an issue of DNA encoding specifying an amino-acid sequence as determined by the genetic code"); *id.* at 1059: 16-21 (stating that "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" refers to "the DNA sequences that encode all of the amino acids from +1 to +166 of the EPO sequence"); *id.* at 1063: 17-19 (explaining that "DNA encoding" refers to DNA in the cell, not to "the polypeptide that is ultimately secreted by the cell. It's a statement of the coding capacity of the DNA in the cell"); *id.* at 1055: 13-18 ("It simply refers to a sequence of DNA which has the capability of encoding, which encodes, a particular protein. It is not a statement about a protein that the cell actually makes or secretes."). Indeed, even Dr. Kingston, HMR/TKT's expert, admitted that one way the word "encoding" "could be used very precisely is to describe a very, very precise small bit of the gene, and that is the codons." Kingston Test., R. Trial Tr. at 163: 2-16.[50] Further, consistent with Dr. Lodish's testimony, Dr. Kingston stated that the phrase "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" means "DNA that provides the instruction to make th[e] protein which would be the sequences" found in Figure 6 and depicted as the codons encoding amino acids +1 through +166. Kingston Test., R. Trial Tr. at 135: 2-142: 7 (circling the entire sequence

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[49] "RNA" is short for "ribonucleic acid."

[50] Dr. Kingston explained that the other "perfectly valid" way the word can be used, depending on the context, is to "describe all the instructions to make the mature protein." Kingston Test., R. Trial Tr. at 163: 7-12. In other words, Dr. Kingston testified that the term can also mean that it provides all the instructions necessary to allow a certain protein to be made.

of Figure 6); Lodish Test., R. Trial Tr. at 1059: 22-1060: 25 (same).

Again, however, none of this evidence is necessary to the Court's construction because an examination of the plain and ordinary meaning of the words, the claims themselves, and the specification demonstrates that HMR/TKT's asserted construction is off base. *Vitronics*, 90 F.3d at 1582; *SRI Int'l*, 775 F.2d at 1118; *Autogiro*, 384 F.2d at 397.[51]

a. The Plain and Ordinary Meaning

The plain and ordinary meaning of "encode" is to "convert from one system of communication to another" and "to convert (a message) into code." *Webster's Ninth New Collegiate Dictionary* 1990. This implies that "DNA encoding" is DNA that converts one type of message or text into another type of message and that it provides information to the cell.

b. The Claims

The claim language supports the plain and ordinary meaning of the term. The claim language establishes that "DNA encoding" refers to DNA that contains a certain sequence in the cells. Both claims 4 and 6 describe processes for producing a glycosylated erythropoietin polypeptide. The sentences in section (a) of the disputed claims do not, as HMR/TKT argues, require the production of the end-product of the claimed processes—an EPO polypeptide with 166 amino acids. To the contrary, the claims clearly distinguish between the cells grown in step (a) (which comprise "DNA encoding the mature erythropoietin amino acid sequence of Figure 6") and the EPO glycoprotein itself that is isolated in step (b). Here, the "mature erythropoietin amino acid sequence of FIG. 6" modifies "DNA encoding" in the cells grown in step (a)—not the "glycosylated erythropoietin

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[51] Neither party directed the Court to the prosecution history. Therefore, the Court will not look to it to construe the disputed term.

polypeptide" isolated in step (b). Therefore, based on the claim language and the ordinary meaning of the words, it appears that the sentences containing the disputed phrase mean, in conjunction, that the DNA must provide or contain the code or instructions for the "mature erythropoietin amino acid sequence of FIG. 6."

The claims do not, however, imply that a protein with the "mature erythropoietin amino acid sequence of FIG. 6" must at the end of the process be produced. This point becomes clear when comparing these claims to that of the '080 patent. The '698 claims recite a "DNA *encoding* the mature erythropoietin amino acid sequence of FIG. 6." as opposed to the claims of the '080 patent that specifically recite an *EPO glycoprotein* that "comprises the mature erythropoietin amino acid sequence of FIG. 6." '080 Patent, Ex. 1, col. 38: 42-43.

In a nutshell, HMR/TKT's construction conflates the concept of DNA that encodes for a protein with requiring the production of a specific protein and in so doing ignores how proteins are actually produced. The DNA encodes the protein. It provides the instruction set used by the *cell* to synthesize a polypeptide that is later processed to its final form. DNA encoding a specific amino acid sequence, however, does not necessarily determine the final length of the polypeptide produced by the cell. The testimony adduced at trial regarding the 166th arginine makes this clear. Dr. Lodish explained that "as long as that DNA encodes the mature erythropoietin—mature EPO sequence, it matters not at all how many other amino acids might be there. Whatever it is, as long as it encodes that sequence, it's fine." Lodish Test., Trial Tr. at 248: 23-249: 1.

HMR/TKT counterargues that it is the protein that is produced by the cell that determines what instructions were actually present in the cell *and used* in the process, that is, that erroneous instructions are not really instructions at all. *See, e.g.*, 7/28/03 Hr'g Tr. at 52: 1-9 (explaining that "there's no proof one way or another as to what the intermediary

is," and "the only proof that there is in this case is as to the end product").[52]

The Court, however, is not persuaded. The evidence adduced at the first trial overwhelmingly suggested that although the DNA encodes for a 166 amino acid sequence, ultimately, the *cell* cleaves off the last amino acid residue prior to secretion of the final protein, EPO that has a 165 amino acid sequence. *Amgen I*, 126 F. Supp. 2d at 86, 101; Lodish Test., Trial Tr. at 347: 16- 18, 348: 3-9; 7/28/03 Hr'g Tr. at 52: 1-9. As Amgen's counsel explained at the *Markman* hearing, "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" is DNA containing codons for amino acids 1-166 of FIG. 6. These instructions will be used by the cell to produce a 165 amino acid erythropoietin. 7/28/03 Hr'g Tr. at 44: 11-47: 11.[53] Thus, DNA can encode or

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[52] HMR/TKT believes it somehow bolsters its argument by pointing out that the Court construed the word "mature" to mean the "*fully realized* form of the amino acid sequence of Figure 6," *Amgen I*, 126 F. Supp. 2d at 87 (emphasis). This argument, however, fails to persuade the Court, for it does not change the definition of DNA encoding, it merely refines what is being encoded.

[53] Amgen's counsel provided a brief, undisputed, refresher for the Court as follows:

> [T]he DNA encodes EPO. The DNA is transcribed to make a messenger RNA. That messenger RNA is then reprocessed in the cell. That messenger RNA is extruded from the nucleus. A ribosome binds to it, translates the messenger RNA into a protein. And a protein that is a copy of the entire DNA sequence of the messenger RNA, including both the leader sequence and the . . . amino acid position 166, is made in the cell. The cell then . . . further processes that protein cutting off . . . the leader sequence of the protein and the amino acid at 166, and that is done before the cell then secretes the fully processed form of the hormone. . . . And as the protein is secreted from the cell, even though it's encoded by DNA that has 166 amino acid, the cell actually produces a protein that has 165 amino acid.

7/28/03 Hr'g Tr. at 45: 21-46: 12.

provide the genetic instructions for a protein that when ultimately secreted has a structure different from the one that the instructions dictate. That some of these instructions are not in the end "used" does not erase the fact that the DNA contained the information in the first place.

Moreover, as Amgen argues, HMR/TKT's construction makes the claims illogical. With HMR/TKT's construction, the claimed processes would require the use of a cell containing "a promoter DNA operatively linked to an EPO protein" or "an amplified EPO protein." Amgen's Mem. In Opp'n re '698 [Doc. No. 717] at 6-7. As asserted by Amgen and undisputed by HMR/TKT, this does not make sense.

In sum, any argument based on the claims that the words "producing" or "that produces" should be inserted in lieu of "encoding" fails along with HMR/TKT's argument that "encoding" refers to the EPO protein itself.[54]

c. The Specification

Like the claims, the specification supports the plain and ordinary meaning of the word "DNA encoding." It demonstrates that one skilled in the art at the time would have defined "encoding" as providing genetic instructions, that is, the sequence.

At the *Markman* hearing, HMR/TKT pointed to columns 11 and 13 in the specification to support its argument that DNA encoding means producing or that the protein is

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[54] It is true that the Court construed the term "mature erythropoietin amino acid sequence of FIG. 6" in the '080 patent to refer to the structure of the claimed EPO glycoprotein. In the '698 patent, however, the claims refer to the structure of the DNA, not of a protein.

actually produced. 7/28/03 Hr'g Tr. at 51: 6-11. Those sections state that:

> The isolation of the desired cDNA clones containing EPO encoding DNA was accomplished through the use of DNA/DNA colony hybridization.

'933 Patent, Ex. 1, col. 13: 64-66.

> Specifically comprehended in part (b) are genomic DNA sequences encoding allelic variant forms of monkey and human erythropoietin and/or encoding other mammalian species of erythropoietin. Specifically comprehended by part (c) are manufactured DNA sequences encoding EPO, EPO fragments and EPO analogs which DNA sequences may incorporate codons facilitating translation of messenger RNA in non-vertebrate hosts.

'933 Patent, Ex. 1, col. 11: 54-61.

As this Court pointed out during the hearing, however, neither of these sections equates "encoding" with producing. 7/28/03 Hr'g Tr. at 51: 12-15. Likewise, neither shows a clear and deliberate attempt by the patentee to become its own lexicographer. *See Renishaw*, 158 F.3d at 1249; *Vitronics*, 90 F.3d at 1582; *Altiris*, 318 F.3d at 1370; *Teleflex*, 299 F.3d at 1326. Each can be read consistently with the ordinary and customary meaning as understood by one skilled in the art, that is, inserting "providing the genetic instructions for" in lieu of "encoding." In fact, the section to which HMR/TKT points in column 11 works against its argument that "DNA encoding" means DNA producing the actual protein because it refers to DNA sequences encoding EPO and EPO fragments. Under HMR/TKT's construction, this section would require EPO fragments actually to be produced instead of requiring that the DNA have the genetic instructions for, that is, provide the codons or genetic sequence for, EPO fragments.

5. Conclusion and Claim Construction of "DNA Encoding"

Accordingly, the Court construed "DNA encoding" to mean "the genetic instructions for." 7/28/03 Hr'g Tr. at 56: 18-23.[55] TKT/HMR, however, did not give up. As a last-ditch effort to win on literal infringement—which is what claim construction is really all about—HMR/TKT argued at the second trial via Dr. Kingston's testimony that "genetic instructions for," the Court's construction of DNA encoding, could mean either the codons for the amino acids plus 1 to 166 of Figure 6 of the patent, or alternatively, all the instructions to make the mature protein including the regulatory sequences. Kingston, R. Trial Tr. at 161-163. Dr. Kingston explained that a scientist could use the term differently depending on the context. *Id.* To be clear, in this context, the Court interprets the claim to be referring to the coding sequence, the piece of DNA that actually specifies the amino acid sequence—not the regulatory sequences that determine when and under what conditions the cells copy the gene into RNA.[56] This interpretation is supported by the claims themselves, which refer to DNA that encodes—provides the genetic instructions for—"the mature erythropoietin amino acid sequence of FIG. 6." Figure 6 indeed depicts, among

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[55] The Court noted that this construction applied any time DNA encoding was used throughout the various claims. 7/28/03 Hr'g Tr. at 56: 18-23.

[56] Dr. Lodish and Dr. Kingston appear to agree that there are two parts to genes. "One is the regulatory sequences that determine when and under what conditions the cells copy the gene into RNA; and the second is the coding sequence, the piece of DNA that actually specifies the amino acids in the encoded product." Lodish Test., R. Trial Tr. at 1058: 20-25. They disagree about to what this claim is referring. Interestingly, at the same time that Dr. Kingston claims that this Court's construction means the regulatory sequences—all the instructions for the protein—he admits that "[t]he DNA that encodes each amino acid is the same" in both Amgen's and HMR/TKT's cells. Kingston Test., R. Trial Tr. at 162: 18-19.

other things, the deduced amino acid sequence that is arrived at by reading the codons of the DNA encoding the protein. Importantly, HMR/TKT points to no support in the prosecution history for its argument on this point. Thus, the Court interprets the claims to require the use of cells containing DNA that provides the genetic instructions, the codons, for a 166 amino acid sequence.

C. Are Claims 4 and 6 of the '698 Patent Step-Plus-Function Claims?

1. Background[57] and Summary of The Parties' Arguments

Whether Amgen, in referring to the "step[] of . . . growing under suitable nutrient conditions" in claims 4 and 6 of the '698 patent, was making step-plus-function claims is an issue raised for the first time by HMR/TKT in its Memorandum in Opposition to Amgen's Renewed Motion for Summary Judgment of infringement of claims 4-9 of the '698 patent. HMR/TKT's Mem. In Opp'n re '698 [Doc. No. 700] at 9. Paragraph 6 of 35 U.S.C. § 112, which sets forth the notion of step-plus-function and means-plus-function, "obligates this court to interpret each functional element in a combination claim by reference to the corresponding structure, material, or acts described in the *specification and their equivalents*." *Seal-Flex, Inc.* v. *Athletic Track and Court Const.*, 172 F.3d 836, 843 (Fed. Cir. 1999) (emphasis added); *O.I. Corp.* v. *Tekmar Co., Inc.*, 115 F.3d 1576, 1583 (Fed. Cir. 1997).[58] In

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[57] For more background, see background discussion regarding construction of the term "DNA encoding."

[58] The purpose of section 112, paragraph 6 was

> to permit use of means expressions without recitation of all the possible means that might be used in a claimed apparatus. . . . The price that must be paid for use of that convenience is limitation of the claim to the means specified in the written description and equivalents thereof. Similarly, a step for accomplishing a particular function in a process claim may also be claimed without specificity subject to the same price.

O.I. Corp., 115 F.3d at 1583 (internal citations omitted).

other words, if this section applies, the Court must limit its infringement analysis to a comparison of the type of "growing" claimed in the *specification* to the type of growing utilized by HMR/TKT.

Ironically, this is exactly what the Court did—*in error*—in the first go-round. In *Amgen I*, the Court based its holding of non-infringement of the '698 patent on a comparison of HMR/TKT's process to the processes outlined in the patent specification.[59] This was error because the Court had never ruled that the relevant claims qualified as a step-plus-function claims.[60] HMR/TKT now presses the Court to address the issue and so to rule.

The wrinkle here is whether the Court now can address this issue—that is, whether the Court can or should permit HMR/TKT to raise the argument at this stage. After all, in 2000, the Court issued a sanction order against HMR/TKT limiting it to the contentions specifically described in its responses to interrogatories. Amgen's Mem. in Opp'n re '698 & '349 [Doc. No. 717] at 4; Amgen's App. to Mem. in Opp'n re '698 & '349 [Doc. No. 719], Ex. A (1/28/00 Order Granting Sanction). HMR/TKT never identified its step-plus-

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[59] The Court compared the accused process to the preferred embodiment in the claim and concluded that "HMR/TKT's process for producing erythropoietin differs markedly from that disclosed by Amgen's specification" because it "utilizes the endogenous rather than exogenous EPO gene" and it "places it promoter upstream from rather than adjacent to the EPO gene." *Amgen I*, 126 F. Supp. 2d at 122.

[60] In other words, the Court went straight to a step-plus-function approach without first ruling that these were indeed step-plus-function claims. As will be discussed *infra*, the Court mentioned to the parties when giving a ruling of non-infringement of the '698 patent, that it was considering a means-plus-function type of analogy. When writing the opinion, however, the Court did not address whether step-plus-function claims were indeed involved and, despite any discussions to the contrary, did not base its ruling of non-infringement of the '698 patent on a finding that it involved step-plus-function claims.

function theory in its responses to Amgen's contention interrogatories as a basis for non-infringement of the '698 patent. Amgen's App. to Mem. in Opp'n re '698 & '349, Tab C (12/7/99 HMR/TKT's Supplemental Answers and Objections to Amgen's Interrog. Nos. 2, 3, and 9) at 5-7, 17. Moreover, HMR/TKT never stated that this aspect of the '698 patent (i.e., whether it included a step-plus-function claim) needed to be resolved through a *Markman* hearing. Amgen asserts that the Court should therefore not allow this argument, and, at a minimum, the Court should afford Amgen the opportunity to present evidence directed to this new step-plus-function argument. *Id.* at 4-5. Moreover, Amgen argues that even if the Court allows such an argument, it lacks merit because "growing" is an "act," not a "function."

2. Discussion[61]

a. Should the Court Allow HMR/TKT to Make Its Step-Plus-Function Argument?

Whether the language of a claim is in step-plus-function format is a question of claim construction. *See, e.g., Kemco Sales, Inc.* v. *Control Papers Co., Inc.*, 208 F.3d 1352, 1360 (Fed. Cir. 2000) ("Whether the language of a claim is to be interpreted according to 35 U.S.C. § 112, ¶ 6, i.e., whether a claim limitation is in means-plus-function [or step-plus function] format, is a matter of claim construction and is thus a question of law, reviewed de novo."); *Personalized Media Communications, LLC* v. *Int'l Trade Comm'n*, 161 F.3d 696, 702 (Fed Cir. 1998) ("An infringement analysis entails two steps. . . . The first step, claim construction, is a question of law which we review de novo. . . . The second step is factual. . . . Whether certain claim language invokes 35 U.S.C. § 112, ¶ 6 is an exercise in claim construction and is therefore a question of law." (citations and internal quotation

[61] See the preceding section regarding "DNA encoding" for recitation of claims 4 and 6 of the '698 patent.

marks omitted)). Generally, on appeal, a party cannot proffer a new claim construction that changes its scope, but it can present additional arguments in support of a previously proposed construction. *See, e.g.*, *CCS Fitness, Inc.* v. *Brunswick Corp.*, 288 F.3d 1359, 1371 (Fed. Cir. 2002). The rationale is that the parties deserve notice and an opportunity to develop the record and, at the same time, the appellate court needs to have a properly reviewable record on an issue raised on appeal. *Interactive Gift Exp., Inc.* v. *Compuserve, Inc.*, 256 F.3d 1323, 1346-46 (Fed. Cir. 2001); *cf. Finnigan Corp.* v. *Int'l Trade Comm'n*, 180 F.3d 1354, 1363 (Fed. Cir. 1999). Thus, a relevant inquiry in determining whether a new claim construction can be pressed is "whether the trial court and the party claiming waiver had fair notice and an opportunity to address the issue concerning the scope of a claim limitation." *CCS Fitness*, 288 F.3d at 1371.

The situation here is unusual. First, this is not a new claim construction argument raised on appeal but instead a new claim construction argument raised on remand to the trial court. Second, counsel for Amgen—the party now seeking to have the issue deemed waived—acknowledged the possible applicability of the step-plus-function doctrine to the Court. On June 9, 2000, after the Court made its finding of non-infringement of the '698 patent, Amgen queried whether the Court was construing the '698 process claims as "means plus function" claims. Trial Tr. at 1308-1309. The Court replied as follows:

> I don't mean to be elliptical. That is my analogy. That's right. . . . Now I think you've missed on the '698 patent. I think that because I do think you have to spell out a means-plus-function. And I have read this patent with great care and I've reflected on it throughout the

> testimony of all the witnesses. I don't see either by equivalent or by literal infringement.

Trial Tr. at 1309-1310. Thus, the Court referred to the means-plus-function doctrine in relation to the '698 patent[62] but, as noted earlier, did not definitively rule that the asserted claims were in means or step-plus-function format nor even mention stepplus-function in the opinion despite applying the infringement analysis required when a claim is in step-plus-function format.

Although the situation is not straightforward, it is clear that Amgen was on notice of the issue but did not get an opportunity to argue it. Given the procedural posture of the case with respect to the '698 patent specifically, Amgen was fully afforded the opportunity during the remand trial to address the issue, which substantially reduces any prejudice to it.

Indeed, the Federal Circuit has suggested that it is appropriate to consider whether a claim is in means-plus-function or step-plus-function format even when one party has essentially waived the issue. *Rodime PLC* v. *Seagate Technology, Inc.*, 174 F.3d 1294 (Fed. Cir. 1999). In that case, the parties contested at trial whether the plaintiff's claim was in means-plus-function format, with the plaintiff arguing that it was not. *Id.* at 1302. The district court ruled that the claim was in means-plusfunction format. *Id.* The plaintiff appealed, but did

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[62] The fact that Amgen's counsel and the Court referred to "means-plus-function" as opposed to "step-plus-function" makes little difference in the Court's analysis here because the two concepts are very closely related, enough so that mention of one provides notice of the potential that the other may apply. *Seal-Flex*, 172 F.3d at 848 (noting that although they require distinct analyses, they are similar and that 35 U.S.C. § 112 ¶ 6 suggests a strong correlation between the two); *see also O.I. Corp.*, 115 F.3d at 1583. To that end, the Federal Circuit has suggested using means-plus-function case law to "give guidance for determining whether a claim element is in step-plus-function form so as to invoke the statute's claim interpretation requirements." *Seal-Flex*, 172 F.3d at 848.

not press that particular issue and thus apparently conceded that the claim was in means-plus function format. *Id.* The Federal Circuit nonetheless assessed *de novo* whether the claim was indeed in means-plus-function format, explaining that:

> [The plaintiff's] concession . . . does not relieve this court of its responsibility to interpret the claims as a matter of law. To interpret the claims, this court must decide the subsidiary question of whether the claim element disputed by the parties invokes § 112, ¶ 6 in the first instance. . . . Only by undertaking this inquiry can this court ensure consistency in statutory application. Moreover, this court's claim interpretation affects entities beyond the parties to this case. Therefore, this court examines the district court's decision that this claim falls under § 112, ¶ 6.

Id. (internal citations omitted). The Federal Circuit subsequently concluded that the district court had erred and that the claim was not in means-plus-function format.

Similarly, in this case, whether this portion of the '698 patent is in step-plus-function format determines the entire analytic framework for analyzing whether HMR/TKT's process infringes this part of the patent. To make this assessment, therefore, this Court needs to determine which analytic framework is implicated. The Court can either make this decision on the merits or can simply decide that the regular infringement framework must be used because HMR/TKT waived its argument that the step-plus-function framework should be used. The problem with the latter approach is that, if the step-plus function framework is truly the applicable one, and the Court nonetheless declines to use it on grounds of waiver, the Court will essentially be applying the wrong law to this aspect of the claim. This, in turn, undermines consistency in statutory application.

For these prudential reasons, this Court analyses whether claims 4 and 6 of the patent are step-plus-function claims. It does so in the course of construing the claims because, as noted above, whether the language of a claim is in step-plus-function format is a question of claim construction. *See, e.g., Kemco Sales, Inc.*, 208 F.3d at 1360; *Personalized Media Communications, LLC*, 161 F.3d at 702.

b. Are Claims 4 and 6 of the '698 Patent Step-Plus-Function Claims?

This is a close question, but, on balance, claims 4 and 6 of the '698 patent do not qualify as step-plus-function claims.[63] Five reasons support this conclusion.

First—although this is not dispositive—the words "steps of" are used in the claim. Such a grammatical structure indicates that this is not a step-plus-function claim, because the phrase "steps of" colloquially signals the introduction of specific acts, rather than functions. *See Seal-Flex*, 172 F.3d at 850 ("[T]he . . . phrase 'steps of' tend[s] to show that § 112, ¶ 6 does not govern that limitation. Accordingly, this court has similarly denied step-plus-function treatment to method claims which use the conventional 'steps of' language."); *see also O.I. Corp.*, 115 F.3d at 1582-83; *Serrano* v. *Telular Corp.*, 111 F.3d 1578, 1583 (Fed. Cir. 1997). Similarly, Amgen did not use the phrase that typically signals the introduction of a step-plusfunction limitation: "step for." *See Seal-Flex*, 173 F.3d at 849 (Rader, J., concurring); *Masco Corp.* v. *United States*, 303 F.3d 1316, 1326-27 (Fed. Cir. 2002). Accordingly, there is a presumption that section 112, paragraph 6 does not apply, that is, that this is not a step-plus-function claim. *Generation II Orthotics Inc.* v. *Med. Tech. Inc.*, 263 F.3d 1356, 1368 (Fed. Cir. 2001).

Second, upon examination, the claim element "growing" appears to recite a specific act for performing an ultimate

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[63] Thus definitive resolution of the procedural dispute is unnecessary.

function, that is, it appears to explain how the function is accomplished, rather than reciting the ultimate function itself. This is a key distinction. As Judge Rader explained in his concurrence in *Seal-Flex*, "the 'underlying function' of a method claim element corresponds to *what* that element ultimately accomplishes in relationship to what the other elements of the claim and the claim as a whole accomplish. 'Acts,' on the other hand, correspond to how the function is accomplished." *Seal-Flex*, 172 F.3d at 849-50. Here the "what" that is ultimately accomplished is the production of glycosylated erythropoietin, and the "how" is "growing [vertebrate cells] under suitable conditions."[64] The dictionary definition of "growing" supports the interpretation that this is an act. *Masco*, 303 F.3d at 1327 (looking to a mechanical

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[64] Expert testimony by one skilled in the art—extrinsic evidence which the Court need not to resort—implicitly supports defining "growing" as an act. Dr. Tlsty made clear that the term "growing" was one that was easily understood by one skilled in the art when he stated, without explanation, that he has "been growing and culturing cells since [he] was an undergraduate." Tlsty Test., Trial Tr. at 832: 11-16; *cf. Greenberg* v. *Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1582 (Fed. Cir. 1996) (stating in the means-plus-function context that "[w]hat is important is . . . that the term, . . . has a reasonably well understood meaning in the art"); *see also Watts* v. *XL Sys., Inc.*, 232 F.3d 877, 881 (Fed. Cir. 2000); *Caterpillar Inc.* v. *Detroit Diesel Corp.*, 961 F. Supp. 1249, 1256 (N.D. Ind. 1996) (quoting *Greenberg*, 91 F.3d at 1583 ("The acts set forth in Claim 1's elements are 'functional' only in the manner in which all acts are functional, and nothing before the court suggests that the acts set forth in the claim lack a 'reasonably well understood meaning in the art.'").

The way in which HMR/TKT described the culturing and growing of its cells in Investigational New Drug Application ("IND") for HMR 4396 provides further evidence that the term has a reasonably well-understood meaning in the art. For example, it stated that "[C]ells grown as attached cultures in static flask were released by trypsination. The cells were resuspended in LONZA Biologics proprietary HM9 Serum-free medium . . . . Once a reliable pattern of growth was established, the serum supplement was progressively eliminated from the medium." Amgen's App. to Mem. in Opp'n re '698 & '349, Tab T (Ex. 19, IND for HMR 4396) at 574.

engineering dictionary and a regular unabridged dictionary to determine whether "transmitting" is an act); *Vitronics*, 90 F.3d at 1584 (noting that judges are free to consult technical treatises and dictionaries "so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents"). Here, the dictionary definitions of growing are "to increase in size by a natural process" or "to develop and reach maturity." The *American Heritage Dictionary, supra*, at 579. These definitions support that growing is an act. Moreover, they do not contradict the meaning of "growing" that may be inferred from the prosecution history, and HMR/TKT does not argue that Amgen defined the term to have anything other than its plain and customary meaning.

Third, HMR/TKT does not even attempt to explain, much less show, how Amgen's language—"growing under suitable nutrient conditions"—fails to describe an act. "[W]here a method claim does not contain the term 'step[s] for,' a limitation of that claim cannot be construed as a step-plus-function limitation *without* a showing that the limitation contains no act." *Masco*, 303 F.3d at 1327 (emphasis added). To the contrary, HMR/TKT makes only a half-hearted assertion—in a footnote in a memorandum in opposition—that these claims are in step-plus-function format. Indeed, the footnote merely states that the argument HMR/TKT made with reference to claim 7 of the '349 patent can be applied to claims 4 and 6 of the '698 patent. HMR/TKT's Mem. In Opp'n re '698 at 9 n.**.[65] HMR/TKT does not dispute Amgen's evidence, but simply claims that "growing" is not an act. HMR/TKT contradicts itself, however, as it implicitly refers to "growing" as an act in the Corrected Joint Pretrial Memorandum when it admits that HMR 4396 is produced by "growing, under suit-

[65] As will be discussed, HMR/TKT made a more detailed argument that claim 7 of the '349 patent is a step-plus-function claim. This argument fails, however, so it also fails when applied to the '698 patent.

able nutrient conditions R223 cells." Amgen's App. to Mot. for Judgment re '349 [Doc. No. 676], Tab M (4/26/00 Corrected Joint Pretrial Mem.) ¶ 25. This implies that "growing . . ." is not in step-plus-function format. If "growing" was a function and needed further explanation, arguably HMR/TKT would not have admitted to such a statement in the Joint Pretrial Memorandum—at least not without further explanation. HMR/TKT cannot merely assert that there is "no act" contained in this part of the claim without producing some evidence that there is not, i.e., that growing is not an act. *Celotex Corp.* v. *Catrett*, 477 U.S. 317, 324 (1986) (quoting Fed. R. Civ. P. 56(e)) (stating that the non-moving party must "go beyond the pleadings, and by [its] own affidavits, or by the 'depositions, answers to interrogatories, and admissions on file,' designate 'specific facts showing there is a material issue for trial'"); *Seal-Flex*, 172 F.3d at 849-50 (noting that step-plus-function applies only when the "limitation contains nothing that can be construed as an act").

Fourth, the Federal Circuit has made clear that "claiming a step by itself, or even a series of steps, does not implicate section 112, ¶ 6," and that courts must be

> careful not to extend the language of this provision to situations not contemplated by Congress. If we were to construe every process claim containing steps described by an "ing" verb, such as passing, heating, reacting, transferring, etc. into a step-plus-function limitation, we would be limiting process claims in a manner never intended by Congress.

O.I. Corp., 115 F.3d at 1583. If the Court were to construe this process claim that begins with "growing"—an "ing" verb very much like heating, reacting, or transferring—as a step-plus-function limitation, it would be doing just that, that is, limiting the process claims in a manner never intended by Congress. Moreover, the Court would be "render[ing] the scope of coverage of these method claims uncertain and

disrupt[ing] the patentees' settled expectations regarding the scope of their claims." *Masco*, 303 F.3d at 1327 (noting that "method claims are commonly drafted . . . by reciting the phrase 'steps of' followed by a list of actions comprising the method claimed").

As a final matter, the Federal Circuit's silence as to whether these claims are step-plus-function claims may be indicative. True, the Federal Circuit probably may not even have considered the possibility.[66] Alternatively, however, the Federal Circuit may have considered the step-plus-function possibility but rejected it as without merit. This latter interpretation of the Federal Court's silence is supported by the Federal Circuit's statement that this Court's analysis (comparing HMR/TKT's process to the specification) was "legally unsupportable." *Amgen II*, 314 F.3d at 1350-51. If the analysis was "legally supportable" by, for example, a finding that the claim was in step-plus-function format, the Federal Circuit certainly could have reached in and decided the issue itself, *see Rodime*, 174 F.3d at 1294. While it is true that in *Rodime*, the issue had been squarely before the district court and thus apparent to the Federal Circuit, here the issue was flagged by the way this Court erroneously conducted its infringement analysis. To anyone familiar with patent law, step-plus-function would have come to mind upon reading the Court's infringement analysis which limited Amgen's processes to those outlined in the specification. That the Federal Circuit failed to address the issue may, therefore, be significant. *Ethicon Endo-Surgery, Inc.* v. *U.S. Surgical Corp.*, 93 F.3d 1572, 1582 (Fed. Cir. 1996) ("We must affirm the decision of the district court if it is supported by any ground properly preserved on appeal."); *Datascope Corp.* v. *SMEC Inc.*, 879 F.2d 820, 822 n.1 (Fed. Cir. 1989) ("Appellees

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[66] The issue was likely never brought to the Federal Circuit's attention since neither party, on appeal, had anything to gain in bringing it up.

always have the right to assert alternative grounds for affirming the judgment that are supported by the record.").

3. Conclusion and Claim Construction

Though it is a close question, this Court rules that claims 4 and 6 of the '698 patent, in referring to the "steps of: (a) *growing under suitable nutrient conditions . . .*," are not step-plus-function claims and that the regular infringement framework should therefore apply.

D. Is Claim 7 of the '349 Patent a Step-Plus-Function Claim?

1. Background

Amgen's '349 patent contains six product claims (claims 1-6) and one process claim (claim 7). '349 Patent, Ex. 1. This Court held, and the Federal Circuit affirmed, that HMR/TKT's HMR 4396 literally infringes the product claims of the '349 patent. *Amgen II*, 314 F.3d at 1352, 1358. Based on a comparison between the accused product and the preferred embodiment, this Court held that HMR/TKT did not literally or equivalently infringe the process claim, claim 7. *Amgen I*, 126 F. Supp. 2d at 122. The Federal Circuit, as it did with the Court's holding of infringement of the '698 patent, vacated this ruling and remanded it so that the Court could analyze infringement by comparing the accused process to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1351, 1347, 1313. Therefore, the remaining issue regarding this patent is whether HMR/TKT's HMR 4396 infringes claim 7.

2. The Claim at Issue

Claim 7 of the '349 Patent:

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.

'349 Patent, Ex. 1, col. 38: 34-36.

3. Summary of the Parties' Arguments

HMR/TKT, in an effort to establish non-infringement of claim 7, has argued, as it did with claims 4 and 6 of the '698 patent, that claim 7 is a step-plus-function claim and that 35 U.S.C. § 112, ¶ 6 therefore applies. As such, it contends that its product does not literally infringe the "step of culturing" because HMR/TKT's process does not involve the culturing procedures set forth in Amgen's specification. HMR/TKT's Mem. In Supp. [Doc. No. 687] at 12-13. As with the '698 patent, Amgen argues, as a preliminary matter, that HMR/TKT is improperly basing its motion under Fed. R. Civ. P. 52(c) on new arguments and defenses, given the previous orders of this Court and Amgen's lack of opportunity to address these issues. Amgen's Mem. In Opp'n re '698 & '349 [Doc. No. 717] at 3-5. Furthermore, Amgen points out, the procedural context here is different than it was with the '698 patent, as this Court heard the entirety of both parties' arguments and evidence concerning '349 claims 1, 3, 4, 6, and 7. Lastly, Amgen argues, for the same reasons that it did regarding the '698 patent, that claim 7 is not a step-plus-function claim. *Id.* at 11-14.

4. Discussion

a. Should the Court Allow HMR/TKT to Make Its Step-Plus-Function Argument?

Here, there is the same wrinkle that there was with the step-plus-function argument respecting the '698 patent: should the Court permit HMR/TKT to raise this argument at this late stage in the game? There are two differences, however, that make the wrinkle, in the context of this patent, harder to iron out. First, the Court did not remark on the record, as it did with the '698 patent, that it was making a means-plus-function analogy in ruling on the '349 patent claims. Second, HMR/TKT has already presented its case of non-infringement regarding all the claims of the '349 patent.

Neither of these differences, however, prevents the Court from allowing HMR/TKT to make this argument at this point. The fact that the Court did not make a means-plus analogy to this patent is easily overcome since the Court, in *Amgen I*, explained that it found non-infringement of claim 7 of the '349 patent for the same reasons as it did the '698 patent. Thus, the parties were on notice that any analysis regarding the process claims of the '698 patent would necessarily apply to the '349 patent. The procedural landscape ought not prevent the Court from construing whether this is a step-plus-function claim. If it is such a claim, the Court ought not conduct its infringement analysis as though it were not. This claim is here on remand and the Court must construe it in accordance with the law. Thus, the Court reaches the same conclusion as it did with the '698 patent, that is, that it can and should address HMR/TKT's step-plus-function argument.

b. Is Claim 7 of the '349 Patent a Step-Plus-Function Claim?

The determination of whether claim 7 of the '349 patent is a step-plus-function claim must be made in the same way as any other determination regarding claim construction. As such, the Court must principally rely on intrinsic evidence and refer to extrinsic evidence only if necessary, with the exception that a dictionary or treatise—which qualifies as extrinsic evidence—can be consulted freely as long as it does not contradict the patent language.

The Court's assessment of whether "culturing" is a function rather than an act, such that the step-plus-function framework applies, tracks the analysis provided above with respect to the whether "growing" is a function rather than an act in the '698 patent. Just as the Court ruled that growing is an act, it rules that culturing is an act, and claim 7, therefore, does not state a step-plus-function limitation.

Like the asserted claims of the '698 patent, claim 7 contains the phrase "step of," rather than the phrase "step for." Accordingly, there is a presumption that section 112, paragraph 6 does not apply—that this is not a step-plus-function. *Generation II Orthotics Inc.*, 263 F.3d at 1368; *Seal-Flex*, 173 F. 3d at 849 (Rader, J., concurring); *Masco*, 303 F.3d at 1326-27.

HMR/TKT argues that "culturing" is the claimed function of claim 7. HMR/TKT's Mem. in Supp. re '698 & '349 [Doc. No. 687] at 13. Specifically, it claims that the "what" is "culturing." In other words, HMR/TKT argues that "culturing" is "what" the claim ultimately accomplishes, and nothing else in the claim describes "how" the culturing is accomplished. HMR/TKT's Reply Mem. re '698 & '349 [Doc. No. 725] at 9. While at first blush this argument makes sense, the Federal Circuit, in *Masco*, interpreted Judge Rader's formulation as requiring analysis of "what th[e] limitations ultimately accomplish in relation to what the other limitations and each claim as a whole accomplish." *Masco*, 303 F.3d 1316. Although there are no words in claim 7 that state the function, as Judge Rader explained in *Seal-Flex*, "the function of that element may nonetheless be discernible from the context of the overall claim and the disclosure in the specification." *Seal-Flex*, 172 F.3d at 850. Here, the claim states in its preamble that it is "a process for producing erythropoietin" suggesting that there is a larger, ultimate function and that "culturing" is merely one act that achieves it. While the "recitation of the overall function of the claim in the preamble does not suffice to convert each element into an act for performing that function so as to preclude application of section 112, paragraph 6," *Seal-Flex*, 172 F.3d at 850,[67] language

[67] Importantly, however, neither is the converse true: the Federal Circuit in *O.I. Corp.*, which dealt with a claim very similar to the claim here, held that "a statement in a preamble of a result that necessarily

in other claims of the patent lends further support to the Court's conclusion that "culturing" is an act. Here, claim 7 itself refers to, *inter alia*, product claims 1 and 4. Claims 1 and 4 describe the purpose of culturing vertebrate cells as being able to produce erythropoietin at a certain rate:

> *Claim 1:* Vertebrate cells which can be propagated in vitro and *which are capable* upon growth in culture *of producing erythropoietin* in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours . . .
>
> *Claim 4:* Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences . . . *for production of human erythropoietin*, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours . . .

'349 Patent, Ex. 1, col. 38: 8-14, 21-27 (emphasis added). Hence, when considering what the "other limitations and each claim as a whole accomplish," it appears that "culturing" is not the claimed function but instead a single step or act of a process claim that "*ultimately accomplishes*" the production of erythropoietin at a certain rate. *Masco*, 303 F.3d at 1327 (emphasis added).

There are two other pieces of support for construing "culturing" as an act. First, both parties agreed that the claim term "culturing under suitable conditions" means "growing in vitro under appropriate [or suitable] conditions." Amgen's App. to Mem. in Opp'n re '698 & '349, Tab P (9/20/99 App. to Amgen's Claim Construction Submission) at 7; *id.*, Tab Q (10/18/99 App. to HMR/TKT's Claim Construction Submission) at 5. Thus, implicitly HMR/TKT admitted that "cultur-

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follows from performing a series of steps does not convert each of those steps into step-plus-function clauses." *O.I. Corp.*, 115 F.3d at 1584.

ing" and "growing" are essentially interchangeable terms. This, considered in combination with the Joint Pretrial Memorandum itself, which states that HMR/TKT's HMR 4396 is produced by "growing, under suitable nutrient conditions R223 cells," 4/26/00 Corrected Joint Pretrial Mem. at 5, ¶ 25, suggests that even HMR/TKT at one point did not believe that "growing"—and by extension, "culturing"—was a function that needed further explanation. This strongly suggests that the term "culturing" was one reasonably well understood by those skilled in the art, a relevant consideration in determining whether a term is an act. *Cf. Greenberg* v. *Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1582 (Fed. Cir. 1996); *see also Watts*, 232 F.3d at 881; *Caterpillar*, 961 F. Supp. at 1256.[68]

Second, dictionary definitions of "culturing" define this word as an act. A standard medical dictionary, *Dorland's Medical Dictionary*, defines "culture" as "propagation of . . . living tissue cells in special media conducive to their growth." Amgen's App. to Mem. in Opp'n re '698 & '349, Tab R (*Dorland's Illustrated Med. Dictionary* (27th ed. 1988)), at 334; *see, e.g., Masco*, 303 F.3d at 1328 (relying on a standard mechanical engineering dictionary definition of "transmitting" to help determine whether it is an act). The *American Heritage Dictionary* describes the verb culturing to mean "to cultivate" or "to develop (microorganisms or tissues, for example) in a culture medium." *The American Heritage Dictionary, supra*, at 348; *see, e.g., Masco*, 303 F.3d at 1328 (relying on standard unabridged dictionary definition of "transmitting" to help determine whether it is an act); *Vitronics*, 90 F.3d at 1584. None of these definitions contradicts what is described in the patent.

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[68] As discussed earlier, expert testimony by Dr. Tlsty and assertions in the IND by HMR/TKT—extrinsic evidence to which the Court need not resort—also support that the terms "growing" and "culturing" have meanings reasonably well understood by those skilled in the art.

In sum, HMR/TKT has failed to show that the "limitation contains nothing that can be construed as an act." *Seal-Flex*, 172 F.3d at 850. On the contrary, "culturing"—that is, developing cells in a certain medium—can logically be construed as an act because it describes *how* the EPO is produced (i.e., by culturing the cells), and because "culturing" is itself a term well understood by those skilled in the art.

As a final matter, the Court notes the same concerns it had with construing "growing" as a step-plus-function limitation. If the Court were to construe "culturing" as a step-plus-function limitation, it would run the risk of interpreting the process claim of the '349 patent in a way that Congress never intended, rendering the scope of coverage of the patent uncertain and disrupting the patentee's settled expectations regarding the scope of the claims. *Masco*, 303 F.3d at 1328; *O.I. Corp.*, 115 F.3d at 1583.

5. Conclusion and Claim Construction

Accordingly, the Court rules that claim 7 of the '349 patent does not contain a step-plus-function limitation and that the regular framework for assessing infringement therefore applies.[69]

IV. VALIDITY CHALLENGES UNDER 35 U.S.C. § 112

When claims are construed broadly, alleged infringers commonly challenge validity under 35 U.S.C. § 112, ¶¶ 1, 2 in light of the broad construction. *Amgen II*, 314 F.3d at 1330. This is exactly what HMR/TKT does here. It argues that certain of Amgen's claims are now invalid because of how broadly the Court construed them. Because these validity challenges relate directly to this Court's claim construction and claims are construed the same way for both invalidity and

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[69] Thus, as with the '698 patent, the procedural dispute and the Court's conclusion as to whether HMR/TKT should be allowed to raise this argument are moot.

infringement, *see, e.g.*, *W.L. Gore & Assocs., Inc.*, v. *Garlock, Inc.*, 842 F.2d 1275, 1279, 1280 (Fed. Cir. 1988), this Court now addresses the relevant section 112 issues before turning to the infringement issues. *See Amgen II*, 314 F.3d at 1330 (addressing section 112 issues before infringement for the same reasons).

As with any validity challenge, the Court begins by presuming that the patents are valid. *Amgen II*, 314 F.3d at 1335; 35 U.S.C. § 282 (2000).[70] As a result, HMR/TKT bears the burden of going forward and a "heavy burden" of persuasion, one that requires proof by clear and convincing evidence. *Amgen II*, 314 F.3d at 1335. Clear and convincing evidence is "evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions is 'highly probable.'" *Buildex, Inc.* v. *Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988).

A. Definiteness

1. The '698 and '349 Patent[71]

a. Discussion

Paragraph 2 of section 112 requires that a patent specification include one or more claims "particularly pointing out and distinctly claiming subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2 (2000). The Federal Circuit has stated that the standard for determining whether a claim is sufficiently definite is "[i]f one skilled in the art would understand the bounds of the claim when read in

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[70] As remarked in *Amgen I*, 126 F. Supp. 2d at 137, the presumption of validity is not a true evidentiary presumption. Instead, it shifts the burden of proof to the non-patent holder and places on it not only the burden of going forward but also the burden of persuasion.

[71] Generally, the Court addresses each argument patent by patent. Where, as here, it makes sense to address more than one patent at once, due to their similarities, the Court will do so.

light of the specification." *Exxon Research and Eng'g Co.* v. *United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001); *Union Pac. Res. Co.* v. *Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001) ("The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification."). Although the definiteness requirement is meant to protect public notice of the scope of the patentee's right to exclude, *Honeywell Int'l, Inc.* v. *Int'l Trade Comm'n*, 341 F.3d 1332, 1338-39 (Fed. Cir. 2003), the Federal Circuit has made clear that the standard for indefiniteness is rather high. A claim is not indefinite merely because its scope is not ascertainable from its face. Instead, it is indefinite if it is "insolubly ambiguous and no narrowing construction can be properly adopted." *Amgen II*, 314 F.3d at 1342; *Honeywell*, 341 F.3d at 1338-39; *Amgen Inc.* v. *Chugai Pharm. Co.*, 927 F.2d 1200, 1218 (Fed. Cir. 1991); *Standard Oil Co.* v. *Am. Cyanamid Co.*, 774 F.2d 448, 453 (Fed. Cir. 1985).

HMR/TKT argues that under the Court's construction of "DNA encoding" the asserted claims of the '698 patent and claim 7 of the '349 patent are invalid as indefinite because they include within their scope many embodiments that will not make EPO. HMR/TKT's Opening Br. After Trial [Doc. No. 808] at 47-48. Specifically, it argues that the Court's construction of the term requires only that the DNA provide the requisite letters or codons, regardless of what protein is actually made, and that the evidence demonstrates that while many cells contain the same DNA codons, only those in which certain particular DNA codons are contiguous will actually produce EPO. Further, it asserts that Amgen has changed its stance and now claims that "genetic instructions for" includes not only the codons but also the splicing instructions for putting those codons together in the correct order.[72]

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[72] The Court notes that it did not construe the term to include the splicing instructions for putting the codons together. That being said, the term

The claims, it asserts, say nothing about splicing instructions or messages and, as such, are indefinite and inoperative.

Amgen responds primarily by arguing that the evidence demonstrates that skilled artisans using the teachings of Amgen's patents would have been able to produce EPO using cells comprising non-contiguous DNA encoding the "mature erythropoietin amino acid sequence of FIG. 6." Amgen's Reply to HMR/TKT's Opening Br. After Trial [Doc. No. 815] at 33-34.[73] Further, it claims that this very evidence establishes that those skilled in the art would have known how to determine which processes fell within the '698 and '349 claims.

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does not occur in a vacuum. It is read with reference to "the mature erythropoietin amino-acid sequence depicted in Figure 6 of the patent." Thus, the claims themselves communicate that other steps are necessary to result in the correct order of amino acids.

[73] Amgen also argues that this Court stated during the 9/18/03 motion hearing that it was not going to address any issues that were not remanded to the Court by the Federal Circuit. Amgen's Reply to HMR/TKT's Findings of Fact [Doc. No. 816] at 173. The issue of infringement, however, was remanded to this Court. A complete decision regarding infringement necessarily includes analysis of these defenses. Moreover, neither party contended that the Court ought not construe "DNA encoding." To the contrary, both parties made it clear this term needed construction. As a result of that construction, a door to a new validity challenge was opened. Thus, to do its job adequately, the Court must address HMR/TKT's challenge.

Additionally, Amgen points out that this Court held that the cell claims (1, 3, 4, and 6) of the '349 patent are adequately described and enabled, and that these rulings are law of the case. Amgen's Reply to HMR/TKT's Opening Br. at n.150. Claim 7 contains a "DNA encoding" limitation only through its dependence from claims 1 and 3. *Id.* As such, Amgen contends, any invalidity challenge to the '349 patent must address the only addition claim 7 makes, which is the "growing step." Thus, Amgen reasons, HMR/TKT's challenge regarding "DNA encoding" should fail. This procedural argument, however, need not be addressed, given the Court's ultimate finding, discussed below, that claim 7 of the '349 patent is not invalid for indefiniteness.

The primary dispute, then, is whether the specification teaches skilled artisans to splice the codons into the correct order when the codons are not contiguous but need to be in order to make EPO. If it does, then the claims are not indefinite as they do not cover embodiments that do not make EPO.

While it may be true, as Dr. Kingston originally stated, that "only those cells in which the DNA letters were contiguous would actually produce EPO," Kingston Test., R. Trial Tr. at 56-60, 164: 2-7, Dr. Kingston admitted that the cells from Example 10 of Amgen's specification produce EPO even though the Figure 6 codons for the mature erythropoietin sequence in the Example 10 cells are not contiguous. *Id.* at 164: 8-22; 170: 4-10. Either Dr. Kingston was blatantly contradicting his original statement, or—as the Court concludes is more likely—Example 10 and Figure 6 communicate to Dr. Kingston, one skilled in the art, how non-contiguous codons can be manipulated to produce EPO. This belies HMR/TKT's argument that the claims are vague or indefinite for not including splicing instructions and for covering contiguous and noncontiguous codons because the specification provides the information that Dr. Kingston believed was missing from the claims.

This deduction—that the specification makes the term "DNA encoding" understandable to the skilled artisan, *Exxon Research and Engineering Co.*, 265 F.3d at 1375; *Union Pacific Resources Co.*, 236 F.3d at 692—is supported by expert testimony from Dr. Lodish and by other testimony from Dr. Kingston.

According to Dr. Lodish, Dr. Lin's patent taught those skilled in the art in 1983 to produce DNA sequences encoding EPO that are either contiguous or *noncontiguous*. Lodish Test., R. Trial Tr. at 1061: 4-1063: 4. In other words, Dr. Lodish testified that those skilled in the art would not consider the phrase "DNA encoding" to require the presence of contiguous codons of the mature EPO sequence of Figure 6.

The main support for this contention stems from the fact that the codons were noncontiguous in Figure 6 of the patent. As mentioned earlier in the claim construction portion of this memorandum and order, Dr. Lodish testified that those of ordinary skill in the art at the time would have understood the disputed term to mean "a DNA which when copied into RNA, and *if necessary* spliced, specifies the order of amino acids that are the mature erythropoietin amino-acid sequence depicted in Figure 6 of the patent." Lodish Test., R. Trial Tr. at 1054: 17-22 (emphasis added); *id.* at 1058: 10-1059: 3. He explained that Figure 6 disclosed to those skilled in the art the codons for the mature EPO amino acid sequence, the introns, exons, and splice donor and acceptor sites of the human genomic EPO sequence. *Id.* Indeed, Dr. Kingston admitted that Lin's specification discloses the EPO gene sequence, the EPO splice donor and acceptor sites, and the linkage of a non-human promoter with the EPO gene. Kingston Test., R. Trial Tr. 116: 23-117: 2. According to Dr. Lodish (and not directly disputed by Dr. Kingston), this information, along with what was known in the art, enabled skilled artisans to alter the codons, to alter or eliminate the introns, and to make many DNA sequences that would encode human EPO and work in the claimed processes. *Id.* Thus, contrary to HMR/TKT's assertions, expert testimony from both sides shows that those skilled in the art would understand the claims to cover contiguous and non-contiguous DNA sequences that when necessary could be spliced into a correct and contiguous order to produce EPO. *Union Pacific Resources Co.*, 236 F.3d at 692 ("The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification.").

b. Conclusion

HMR/TKT has failed to establish by clear and convincing evidence that "DNA encoding" is a vague, ambiguous, or

undefined term not understandable to a skilled artisan when read in light of the specification. Accordingly, the Court rejects HMR/TKT's argument that the disputed claims of the '349 and '698 patent are indefinite.

B. Written Description[74]

1. The '698 and '349 Patents

a. Discussion

The basic requirements for the content of a patent specification are found in 35 U.S.C. § 112, ¶ 1:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . .

35 U.S.C. § 112, ¶ 1 (2000). "The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin* v. *Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). Therefore, the specification must communicate clearly to those skilled in the art that the inventor invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Specifically, the disclosure as originally filed must explicitly or inherently convey to the skilled artisan that the inventor had possession at that time of the later claimed subject matter. *Reiffin*, 214 F.3d at 1346; *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983); *see generally* Guang Ming

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[74] For a discussion of the controversy within the Federal Circuit as to whether section 112 contains a separate written description requirement, or whether it only contains an enablement requirement, see Vernon M. Winters & Elizabeth Stotland Weiswasser, *The Written Description Requirement: Ripe Enough? Or Is More Percolation Required*, Fed. Law., Aug. 2004, at 20.

Whitley, *A Patent Doctrine without Bounds: The "Extended" Written Description Requirement*, 71 U. Chi. L. Rev. 617 (2004). Compliance, however, is to be judged as of the date the application is filed. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1251 (Fed. Cir. 1989); *Application of Koller*, 613 F.2d 819, 824 (C.C.P.A. 1980). Thus, the critical inquiry is whether the specification clearly communicated to those skilled in the art what was claimed based on what was known in the art at the time of the filing—in this case, 1983-84. Only if the claims would have been, at the time of filing, correctly rejected for inadequate support will a court find that the claims are now invalid for lack of support. *See Koller*, 613 F.2d at 824.

HMR/TKT contends that Amgen's claims, as construed by the Court, have a scope far greater than the written description of Amgen's patents and are, therefore, invalid. HMR/TKT's Opening Br. After Trial at 47-48. Primarily, it makes two arguments in support of this contention. First, HMR/TKT argues that the specification "repeatedly describes [the] DNA, cells, processes and proteins in terms of *only* exogenous DNA and heterologous recombination," whereas the Court construed the asserted claims in the '698 and '349 patents to cover both exogenous and endogenous DNA and homologuous and heterologous recombination.[75] HMR/TKT's Opening Br. After Trial at 47-48. Second, HMR/TKT points to the undisputed fact that the specification provides only an example of a process which places the promoter just upstream of the ATG initiation codon of a cloned and isolated EPO gene,

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[75] This is the same argument that HMR/TKT made during the first trial and on appeal with reference to the product claims of the '422 and '349 patents. *Amgen I*, 126 F. Supp. 2d at 149-150, 154 n.51 (rejecting the argument); *Amgen II*, 314 F.3d at 1331 (same). Since the asserted claims of the '698 and claim 7 of the '349 patent are process claims, however, HMR/TKT urges that this argument now has merit and ought be revisited in this context.

although the Court construed "operatively linked," as found in the '698 patent,[76] to cover placement much farther upstream. *Id.*[77] As such, HMR/TKT argues, the asserted process claims of the '698 patent fail to provide adequate written description. *Id.*

(1) HMR/TKT's First Argument: Endogenous DNA and Homologous Recombination

Although HMR/TKT's first argument is, in part, factually correct—the specification explicitly discloses only exogenous EPO DNA expression systems and heterologous recombination techniques[78]—it is misdirected. The section 112 inquiry focuses on what was known by those skilled in the art at the time of the filing of the application. Here, it is undisputed that in 1983-84 (the time period of the application filing date), endogenous activation technology and homologous recombination were not known to skilled artisans. HMR/TKT's Findings of Fact ¶ 488; Amgen's Reply to HMR/TKT's Opening Br. After Trial at 34- 35.[79] Therefore, this technol-

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[76] The term "operatively linked" is not found in the '349 patent, so this argument only relates to the '698 patent.

[77] In *Amgen I*, the Court construed "operatively linked" to mean "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen I*, 126 F. Supp. 2d at 90. It refused to read any distance restriction in the claim term "operatively linked."

[78] As stated in *Amgen I*, experts for both sides agreed that the specification did not explicitly show any examples of human EPO production whereby endogenous EPO DNA was expressed. 126 F. Supp. 2d at 150 n.50. The Court thus inferred that "Amgen did not in fact contemplate applying its techniques to effectuate endogenous DNA expression." *Id.*

[79] HMR/TKT does not dispute Amgen's contentions (see Amgen's Reply to HMR/TKT's Opening Brief After Trial at 34-35) that these are post-filing advancements. Moreover, in making its reverse doctrine of equivalents argument, HMR/TKT asserted that this difference contributed to the Court's finding that HMR 4396 was "technologically advanced."

ogy is irrelevant to the written description analysis, and for good reason. "If later states of the art could be employed as a basis for rejection under 35 U.S.C. § 112, the opportunity for obtaining a basic patent upon early disclosure of pioneer inventions would be abolished." *Application of Hogan*, 559 F.2d 595, 606 (C.C.P.A. 1977); *see also Koller*, 613 F.2d at 825 (same).[80]

HMR/TKT incorrectly assumes that the Court's construction of Amgen's claims to cover this later developed technology changes the analysis. *Application of Koller*, a case similar to this one, shows the fallacy of HMR/TKT's assumption. In that case, the Federal Circuit upheld a broad construction of the term "liquid medium" that covered all solvents (including the later developed water-immiscible solvents) despite a specification that only described water and water-miscible

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HMR/TKT's Mem. in Opp'n re '698 at 6; *see Amgen I*, 126 F. Supp. 2d at 104. Indeed, the Court found in *Amgen I*, and the Federal Circuit affirmed, that endogenous activation was a later-developed technology. *Amgen I*, 126 F. Supp. 2d at 160; *Amgen II*, 314 F.3d at 1334 (noting that Amgen could not have described the endogenous activation method because it was developed 10 years later).

[80] Professor John F. Duffy has recently suggested an intriguing revision to the "prospect theory" of patents, which justifies "prospect patents"—"broad patents issued in the early stages of technical development"—on the ground that they create social benefit by encouraging investment in a technological prospect after the property right has been granted, rather than by encouraging the investment that led to the patent in the first place. John F. Duffy, *Rethinking the Prospect Theory of Patents*, 71 U. Chi. L. Rev. 439, 440 (2004). Professor Duffy agrees that "prospect patents" are socially beneficial in a forward-looking way, but for a different reason: they channel rivalry in such a way that the property right goes to the inventor who is willing to accept the least profit for it. *See id.* at 443-44. Because patents have fixed terms, obtaining a patent earlier in the technological development process means that the period between the date when the patentee can convert the invention into a marketable product and the date when the patent term ends (and hence the period when the property right will actually generate profit) will be shorter. *See id.*

solvents—and not water-immiscible solvents. It reversed, however, the decision of the United States Patent and Trademark Office Board of Appeals that had found, *inter alia*, that the claims failed to provide adequate description. The Federal Circuit conducted its section 112 analysis based on what was claimed and known at the time of the application filing date. Because water-immiscible solvents were not known at the time of the application filing date, the Federal Circuit found that the term "liquid medium" was adequately described. *Koller*, 613 F.2d at 823-25.

Here, the situation is very similar. Because homologous recombination and use of endogenous DNA were not known to those skilled in the art at the time of the application, HMR/TKT's first argument for inadequate written description fails. As the Federal Circuit explained in *Application of Hogan*, "the Courts have consistently considered subsequently existing states of the art as raising questions of infringement but never of validity." *Hogan*, 559 F.2d at 607 (noting that the PTO's concern that allowance of the claims might lead to enforcement efforts against later developers is "both irrelevant and unwarranted" because "[t]he business of the PTO is patentability, not infringement"); *United States Steel Corp.*, 865 F.2d at 1251 (stating that the fact that "claim[s] may cover a later version of the claimed [invention] relates to infringement not to patentability").

HMR/TKT's arguments are more properly reserved for invoking the judicially developed reverse doctrine of equivalents defense which allows interpretation of the claims in light of the specification, *inter alia*, and precludes improper enforcement against later developers. *Hogan*, 559 F.2d at 607. This argument alone fails to establish this defense. Because this is the only argument presented with respect to the sufficiency of the written description of claim 7 of the '349 patent, the Court holds that HMR/TKT has failed to meet its burden with respect to this defense.

(2) HMR/TKT's Second Argument: Placement of the Promoter

HMR/TKT's second argument and Amgen's response thereto, as they relate to the '698 patent, render determination of the written description a bit more squirrelly. As stated above, HMR/TKT correctly argues that the specification only describes insertion of the promoter just upstream of the ATG initiation codon of the EPO gene to be expressed while the Court construed the claims to cover HMR/TKT's process of inserting the promoter far upstream leaving multiple ATGs between the promoter and the gene to be expressed.[81] Instead of counter-arguing, as it did in response to HMR/TKT's first argument, that HMR/TKT's placement technique was a post-filing advance which need not be described, Amgen contends that by 1984, artisans of ordinary skill could have placed a promoter DNA in such a position that multiple ATGs would exist between it and the gene to be expressed, and they knew how to express proteins in vertebrate cells by positioning a promoter upstream of exon coding sequences and removing unwanted DNA by manipulating splice sites. Amgen's Reply to HMR/TKT's Opening Br. After Trial at 34-35; Amgen's Reply to HMR/TKT's Findings of Fact ¶ 67. Further, Amgen asserts, evidence shows that those of skill in the art would have understood the patent to describe operative linkages of far greater distances than 44 pairs and that skilled artisans would have understood from Lin's patent how to avoid potentially interfering ATG sequences and thereby successfully position the promoter further upstream of DNA encoding EPO. *Id.* ¶ 68, ¶ 342.[82]

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[81] *See Amgen I*, 126 F. Supp. 2d at 103-104 (finding that the specification discloses the promoter placement at a position forty-four base pairs from the first codon that expresses the leader peptide leaving only one ATG in the region to be expressed).

[82] Amgen also argues that the Court's findings regarding proximity of the promoter concern the process for constructing cells (cells which been

This argument is curious because the easier path would have been to argue that placement so far upstream was a post-filing advance. Indeed, the Court's factual findings in *Amgen I* would have supported such an argument. *See, e.g., Amgen I*, 126 F. Supp. 2d at 160 (concluding that placing the promoter farther upstream works to make HMR/TKT's process more "technologically advanced" than that in Amgen's patent and commenting that there was no evidence implying that "one of ordinary skill in the art would dare to place a promoter sequence in such a position that multiple ATGs would exist between it and the gene to be expressed"). Such an argument, however, would have weakened Amgen's position with respect to the reverse doctrine of equivalents. In other words, urging that this technique was a post-filing advance would work against Amgen's argument that HMR/TKT's product and process is not so far changed in principal that the Court ought find that it does not infringe under the reverse doctrine of equivalents.

Stuck in a similar catch-22, HMR/TKT argues with respect to section 112 that Amgen should have described upstream placement of the promoter, yet, in furtherance of its reverse doctrine of equivalents argument, HMR/TKT argues with equal passion that a process for producing EPO by linking the promoter and transcription control sequences far upstream of the EPO gene had never been done before HMR/TKT

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held to be adequately described and enabled) and are, therefore, irrelevant to the '698 and '349 claimed processes for producing EPO. Amgen's Reply to HMR/TKT's Opening Br. After Trial at 35; Amgen's Reply to HMR/TKT's Findings of Fact at 41. This argument fails. Just because the cells themselves and the EPO product were found to be adequately described and enabled by the product claims does not mean that the method by which the cells are constructed or the EPO is made is necessarily adequately described and enabled in the process claims. As this Court pointed out in *Amgen I*, "[a] product patent claims a structural entity that, though some process must be undertaken in order to create it, is in no way defined or limited by how it is made." 126 F. Supp. 2d at 101.

developed its patented gene activation process. HMR/TKT's Reply Br. After Trial [Doc. No. 819] at 29, 34. Further, it argues that those skilled in the art recognized that promoter linkages further upstream of the initiation codon would *not* work to produce EPO. HMR/TKT's Findings of Fact ¶ 493. Thus, HMR/TKT's reverse doctrine of equivalents argument belies its argument that Amgen should have described placement of the promoter further upstream of the EPO gene to be expressed since, according to HMR/TKT, this had never been done before. Thus, both parties, to a degree, have argued against their best interests on this issue because to do otherwise would weaken their positions with respect to application of the reverse doctrine of equivalents.

However the parties may frame the issue, this Court, as trier of fact in this case, must determine whether placing the promoter farther upstream was a concept sufficiently known to those skilled in the art at the time of filing such that the claims would have been understood to encompass such a technique. *United States Steel Corp.*, 865 F.2d at 1251 ("'[L]anguage in a specification is to be understood for what it meant to one having ordinary skill in the art at the time the application was filed' . . . and . . . support need be found for only the claimed invention, in view of how one skilled in the art at that time would construe the claims and would read its specification." (quoting *Koller*, 613 F.2d at 824) (internal citation omitted)); *United States Steel Corp.*, 865 F.2d at 1252 (considering the state of the art in 1983-84, the level of sufficiency and the condition of knowledge about all art-related facts at the time of filing).[83] If the Court determines

[83] While the Court found in the first trial that HMR/TKT's promoter placement was a "technological advance" over Amgen's process, the Court notes that it did so in a different context under a different burden of proof and that the ultimate holding of the Court was reversed. In *Amgen I*, the Court held that HMR/TKT had shown by a preponderance of the evidence that its process was substantially different from the process identified in Amgen's '698 patent and claim 7 of the '349 patent. *Amgen I*, 126

that this is so, the Court must consider whether the specification in its entirety—not just literally—conveys to the skilled artisan that Amgen's process includes such upstream promoter placement. *Kaslow*, 707 F.2d at 1375; *cf. Application of Edwards*, 568 F.2d 1349, 1352 (C.C.P.A. 1978).

After careful review of the evidence from the first and second trials, the Court now concludes that placement of the promoter further upstream of the EPO coding region and splicing out deleterious ATGs was indeed a concept known and understood—albeit not practiced—by those skilled in the art at the time Amgen filed its application (1983-84).

Dr. Lodish and Dr. Kingston testified that both Amgen and HMR/TKT use a technique of linking two different pieces of DNA together with a splice donor site and a splice acceptor to express a protein and that this was a standard technique in 1983. Kingston Test., Trial Tr. at 1428-30, 1433, 1434: 12-19; Lodish Test., R. Trial Tr. at 1081 (claiming that at the time of the patent application this type of splicing was common). While Dr. Lodish did indeed admit that Dr. Lin did not know what sequences were upstream of the EPO gene, and

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F. Supp. 2d at 103-104, 122. This ruling was based not only on a finding regarding the promoter placement but also on the finding that HMR/TKT uses homologous recombination as opposed to heterologous recombination. Therefore, the factual finding regarding promoter placement was not alone determinative (as it is here). The Court's legal conclusions based on these factual findings were reversed by the Federal Circuit. Further, the burden here is on HMR/TKT to show by clear and convincing evidence (as opposed to proof by a fair preponderance) that the asserted claims are invalid. Lastly, because the reverse doctrine of equivalents was before the Court for the first time on remand, this Court explained to the parties that it would be evaluating, or rather re-evaluating, the issues involved in such an argument, such as whether placement of the promoter was indeed truly novel. *See* R. Trial Tr. at 1080-81 (noting its previous findings with respect to placement of the promoter, the Court explained that this issue "cuts to the heart" of the reverse doctrine of equivalents and allowed evidence on the issue).

that it was intuitive to place the promoter close to the EPO coding region because the "longer the distance the more problems you're likely to encounter," he clarified that those skilled in the art knew that it was possible to vary the distance and still cause transcription and proteins to be made, because the sequences that are unwanted are readily identifiable and can be avoided. Lodish Test., Trial Tr. at 255-58. Further, he explained, those skilled in the art in 1983 did indeed know that a promoter could be placed 8,000-10,000 bases upstream and that very long intervening sequences could be spliced out. Lodish Test., R. Trial at 1081. Even Dr. Kingston himself admitted that in 1983 those skilled in the art knew how to place a promoter much further upstream than 44 base pairs, the location identified in Example 7 of Dr. Lin's patent. Kingston Test., Trial Tr. at 1436-38.

Additionally, there were published articles showing that those skilled in the art possessed this knowledge. Dr. Kingston's mentor, Dr. Sharp, published an article in 1983 that, according to Dr. Kingston, showed a construct in which a splice donor site was added to splice out approximately a 700 base pair fragment of DNA ("a 5 prime splice and a 3 prime splice") from the message. Kingston Test., Trial Tr. at 1435-36. Indeed, Dr. Kingston himself published an article in 1982 that disclosed that the way to discard a portion of the DNA that was not wanted in the vector was to put a downstream splice receptor or acceptor site and splice it out. *Id.* at 1436-37. In the constructs discussed in the article, the distance between the 5 prime and 3 prime splice sites was, according to Dr. Kingston, between 180 and 500 pairs. *Id.* at 1438.

HMR/TKT argues, however, that the evidence shows that no one had in fact used those splice sites the way that HMR/TKT eventually did—in other words, that placing the promoter upstream as HMR/TKT did was novel. HMR/TKT's Response to Amgen's Findings at 130. HMR/TKT also sug-

gests that the situations to which reference has just been made appear only in nature; that is, they were not human constructs or experiments. *See, e.g.*, Lodish Test., R. Trial Tr. at 1104: 15-1105: 5. The Court is not persuaded that the evidence shows what HMR/TKT claims it does. First, Dr. Sharp's article, Trial Ex. 247, discloses actual experiments showing upstream placement, *see, e.g.*, R. Trial Tr. at 1134-35. HMR/TKT produced no evidence to the contrary. Tellingly, HMR/TKT's counsel neither asked Dr. Kingston whether actual experiments had been conducted in 1983-1984 nor asserted in any of its post-trial memoranda the absence of actual experimentation. Second, and perhaps most enlightening, the only support HMR/TKT offers for its contention that no one skilled in the art had in 1983-84 placed the promoter upstream as HMR/TKT did, or even would have *dared* to do so, is the Court's previous factual findings, which were made with respect to a different legal issue. *See, e.g.*, HMR/TKT's Opening Br. After Trial at 15 (citing only this Court's opinion in support); HMR/TKT's Reply Br. After Trial at 29 (citing this Court's opinion and unsupportive testimony by Dr. Lodish (inaccurately referred to as "Kingston Tr. 162-167") and irrelevant testimony by Dr. Kingston, "Kingston R. Tr. 177, 181"); HMR/TKT's Proposed Findings of Fact ¶¶ 111, 112, 114, 116 (citing this Court's opinion and irrelevant testimony from Dr. Lodish, admitting that he did not include *homologous recombination* in the first edition of his textbook). The Court finds that placement of the promoter further upstream, as HMR/TKT does with its HMR 4396, was a technique known to those skilled in the art at the time of Amgen's application filing.[84]

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[84] In any case, even if the Court were to conclude, as HMR/TKT urges, that no one then had the courage to use the splice sites as HMR/TKT later did, HMR/TKT's written description challenge would still fail; if the courage *and knowledge* had been missing and HMR/TKT's placement of the promoter had been truly innovative and new, then this technique

Because upstream placement of the promoter was known at the time of Amgen's application, however, the Court now addresses whether HMR/TKT has shown by clear and convincing evidence that Amgen did not adequately describe such a placement. The Court agrees with HMR/TKT's central contention that the specification explicitly refers only to placement of the promoter in close proximity (within 44 base pairs) of the EPO gene to be expressed, leaving only one ATG adjacent to the amino terminal coding region. '933 Patent, Ex. 1, col. 24: 15-32. "The test for determining compliance with the written description requirement," however "is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter," rather than the presence or absence of literal support in the specification for the claim language. *Kaslow*, 707 F.2d at 1375; *cf. Edwards*, 568 F.2d at 1352 (noting that in the context of the case before it, "this translates into whether the parent application provides adequate direction which reasonably leads persons skilled in the art to the later claimed compound"). After much reflection and despite some hesitancy, the Court concludes that the disclosure does convey the "later claimed subject matter."

First, as Amgen rightly points out, the '698 claims themselves have no limitations specifying the promoter distance or the number of ATGs. Instead, the claims state that the promoter DNA must be "operatively linked" to the "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." The Court in *Amgen I* construed this to mean "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen I*, 126 F. Supp. 2d at 90.

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would have constituted a post-filing technological advance—something Amgen need not have described in order to satisfy section 112, paragraph 1.

Second, as was determined in *Amgen I*, the specification does not clearly communicate a locational restriction. *Amgen I*, 126 F. Supp. 2d at 90. That the specification recites in one of the examples an exact location for the promoter that is in close proximity to the EPO gene to be expressed is not dispositive. "[T]hat a claim may be broader than the specific embodiment disclosed in a specification is of no moment." *In re Rasmussen*, 650 F.2d 1212, 1215 (C.C.P.A. 1981); *see Gentry Gallery, Inc.* v. *Berkline Corp.*, 134 F.3d 1473, 1480 (Fed. Cir. 1998). As the Court of Customs and Patent Appeals reasoned in *In re Kirschbraun*, 44 F.2d 675 (C.C.P.A. 1930), a court "should never interpret a positively recited generic expression [such as "operatively linked"] to the precise instrumentality disclosed by the patent, except where such narrow interpretation is necessary to distinguish the claim from prior art." *Id.* at 739 (internal citations and quotations omitted).[85]

The only support in the specification that the invention is of a narrower scope than the claims is the absence of specific examples showing an alternate location for the promoter. The specification, however, does not limit the patent to the examples therein. It does not clearly identify placement within 44 base pairs as the only possible location from which to conduct the process nor does it indicate that this exact location was an essential element of the invention or that placement farther upstream is "outside the stated purpose of the invention." *Cf. Amgen II*, 314 F.3d at 1334 (considering these factors); *Gentry*,

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[85] Although the Court intimated in *Amgen I* that the written description requirement may be different for process claims as opposed to product claims, 126 F. Supp. 2d at 150, case law indicates that the written description inquiry is conducted in the same manner regardless of whether the claims address a product or a process. *See, e.g., Rasmussen*, 650 F.2d at 1212 (applying same section 112 analysis to method claim as applied by other courts with respect to product claims); *see also In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976); *Koller*, 613 F.2d at 819.

134 F.3d at 1479 (same); *Ethicon*, 93 F.3d at 1582 (considering whether the aspect was considered an element of the invention and stating that if it was not then the patentee was free to draft the claim broadly). Moreover, the specification does not address possible variations from which the Court could conclude that a further upstream placement was not in the realm of possibility.

That Amgen chose to show placement of the promoter in very close proximity is only evidence that this was perceived to be the best location to achieve operative linkage—as Dr. Lodish testified—not the only location. Lodish Test., Trial Tr. at 258 (explaining that the longer the distance the higher likelihood that problems might occur and that "there's no reason one would want to put it very far upstream. But one could," with a little bit of work); *id.* at 553 (commenting that "in practice in the laboratory one does what is most expeditious"); Lodish Test., R. Trial Tr. at 1131 (explaining that Dr. Lin had no reason even to consider other sequences of pieces of DNA); *cf.* Kingston Test., R. Trial Tr. at 41: 20-21 (testifying that standard practice in 1984 was to place the promoter in a position such that there was not another ATG present). True, Dr. Lodish stated that the patent teaches that by *linking* a strong promoter or *placing it near* the first codon for the signal sequence of EPO, one could overcome the natural suppression of EPO expression in vertebrate cells. Lodish Test., R. Trial Tr. at 1070, 1077- 78. This, however, does not unambiguously limit the location of the promoter to a distance of 44 base pairs or indicate that further upstream placement was not part of the invention. As Dr. Lodish explained, placement of the promoter thousands of base pairs upstream, as HMR/TKT does, is only a "minor difference" that is "irrelevant in the final process." *Id.* at 1077: 1-6.[86] Thus, as

[86] Dr. Lodish also conceded that placement of the promoter can indeed affect expression, Lodish Test., Trial Tr. at 421; *cf.* Kingston Test., R. Trial Tr. at 44: 20-45: 1-5. He clarified, however, that the difference in

testified to by Dr. Lodish, the specification teaches that putting a strong viral promoter upstream of the human EPO gene is the important feature—not how far upstream—as long as the intervening sequences are spliced out. Lodish Test., Trial Tr. at 173, 549; *see also* Lodish Test., R. Trial Tr. at 1081 (noting that "there's nothing different about a large intron spliced out and a small intron spliced out"); *Cooper Cameron Corp.* v. *Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317, 1322-23 (Fed. Cir. 2002) (considering expert testimony on the issue of what the specification teaches). In other words, Amgen's patent teaches that the natural suppression of EPO expression in vertebrate cells can be overcome by *operatively linking* a nonhuman promoter *upstream* of DNA encoding human EPO. *See id.*; *see also* Lodish Test., R. Trial Tr. at 1068: 21-1070: 3.

Therefore, the Court infers that though the examples may show linkage that is *directly* upstream, those skilled in the art would not, nor does the Court, read the specification so to limit the process. *United States Steel Corp.*, 865 F.2d at 1251; *cf. Ethicon*, 93 F.3d at 1582 n.7 (noting that 35 U.S.C. § 112 (1994) allocates to the inventor the task of claiming what the inventor regards as his invention); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1565 (Fed. Cir. 1991) ("There is no legally recognizable or protected essential element, gist or heart of the invention in combination patent. The invention is defined by the claims." (citations and internal quotation marks omitted)). As such, Amgen was free to draft the claim broadly (within the limits imposed by prior art) to exclude the exact placement of the promoter as a limitation of the claimed invention. *Cf. Ethicon*, 93 F.3d at 1582 n.7. "Such a claim is not necessarily unsupported by the specification even though

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expression is determined not by the number of pairs between the promoter and the EPO gene necessarily but by other factors concerning the general area of the chromosome in which it finds itself. Lodish Test., Trial Tr. at 420-421.

it would be literally infringed by undisclosed embodiments." *Id.*

Third, although HMR/TKT has shown that the specification lacks literal support for a process that places the promoter further upstream, it has failed to show by clear and convincing evidence that Amgen's patent does not "reasonably convey to the artisan that [Amgen] had possession at that time of the later claimed subject matter." *Kaslow*, 707 F.2d at 1375 (noting that the presence or absence of literal support in the specification is not determinative). To the contrary, the evidence shows that the specification (both the written words and the figures) discloses the techniques that are employed in a process that places the promoter further upstream such as HMR/TKT does in HMR 4396.[87] It is undisputed that the specification discloses a DNA sequence and the amino acid sequence it encodes, introns, exons, splice donor and splice acceptor sites, and the linkage of a nonhuman promoter with the EPO gene, and communicates that splicing events occur to avoid the deleterious effects of ATGs and to allow the appropriate final functional mRNA to form to produce the amino acids disclosed in Figure 6. *See, e.g.*, Kingston Test., Trial Tr. at 1428-29, 1430; Kingston Test., R. Trial. Tr. at 116: 23-117: 2; *see also* Lodish Test., R. Trial Tr. at 1061: 4-1063: 4. As discussed *infra* with respect to the reverse doctrine of equivalents, the evidence shows (albeit by a slim margin) that HMR 4396 uses the same splice donor and splice acceptor sites as are disclosed in Amgen's specification. Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1-22, 1440: 19-25.[88] HMR/TKT merely copies the

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[87] The Court refers to HMR 4396—as an example of a process that places the promoter further upstream—to support the conclusion that the specification communicates to those skilled in the art a process that incorporates such upstream placement.

[88] While there was much debate about this subject, as discussed in more detail *infra* (parts V.A.3-4, V.B.4), the Court credits Dr. Lodish's

splice donor site and places it upstream of the deleterious ATGs, the intended effect of which is to splice out all the deleterious ATGs that were upstream of the coding region of the EPO gene. *Id.* (explaining that the way the splice donor site is moved is by "ma[king] a design that happens to include the same nucleotides" and "the purpose of that is so that this splice donor . . . would direct a splicing event" that spliced out all of the deleterious ATGs); *see also* Lodish Test., R. Trial Tr. at 1081 ("Very simply put, what [HMR/]TKT did is take this splice donor that's right here, include this G residue directly upstream of it, and move it in toto immediately adjacent to this hGH signal sequences. So in fact, the splicing that occurs . . . in the RNA, between donor 1 and acceptor 1 is identical to the splicing that occurs in . . . Amgen's Example 10 cells."); Lodish Test., Trial Tr. at 174; Lodish Test., R. Trial at 1076: 23-1077: 6; *id.* at 1068-69 (discussing the three principals of Lin's '698 patent). As discussed earlier, placement of the promoter further upstream and splicing out deleterious data was a technique known to skilled artisans in 1983-84. Thus, Amgen's process discloses exactly what HMR/TKT's process does, that is, it discloses locating a strong

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testimony explaining that the exons are not included when one skilled in the art refers to the splice donor and acceptor sites. Lodish Test., R. Trial Tr. at 1107-1110; *id.* at 1132-33 (explaining that it is the splice donor sequence, not the splice junction, that will determine where downstream and with what corresponding DNA downstream a splice junction will splice, and stating that "the splice donor is the sequence . . . that is removed during the splicing process," the splice acceptor is the sequence that is removed downstream, and "it's the regions on either side that are linked together."). There is testimony by Dr. Kingston and evidence from the HMR/TKT's IND that supports this conclusion. As a result, the Court concludes that HMR 4396 uses the same splice donor site as that disclosed in Amgen's specification. Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1-22, 1440: 19-25 (admitting that absent the exons, the splice donor sites were the same and that the intended effect was to splice out what is in between, including intervening sequences and the deleterious ATGs).

promoter upstream of the ATG initiation codon of a cloned and isolated EPO gene (i.e., upstream of the DNA encoding EPO), and splicing out the deleterious data. *Gosteli*, 872 F.2d at 1012 (explaining that the specification must communicate clearly to those skilled in the art that the inventor invented what is claimed).

While it appears that the scope of the right to exclude as set forth in the claims does not overreach the scope of Amgen's contribution to the field of the art as described in the specification, *see Reiffin*, 214 F.3d at 1346, HMR/TKT points to one piece of evidence that suggests the contrary and gives the Court pause. As discussed earlier in a different context, Dr. Lodish admitted that Dr. Lin never even attempted such an upstream placement and did not know what was upstream or downstream of the EPO gene. Lodish Test., R. Trial Tr. at 1129. This, therefore, indicates that Amgen was *not* in *actual* possession of the entire scope of the invention at the time of filing; that is, that Amgen had not, at that time, itself demonstrated though experimentation the distant upstream placement of the promoter.

Although this evidence is compelling, when considered in light of prior case law and HMR/TKT's high burden of proof, it fails to persuade the Court that Amgen's specification is invalid for lack of written description. As discussed, the techniques disclosed in the specification are the same ones used in a process that places the promoter further upstream. Simply because further upstream placement was possible and applicants could have, as testified to by Dr. Lodish, done it and then described it in an example does not mean that the applicant must describe it. This is just the sort of argument rejected in *In re Vickers*, 141 F.2d 522, 988 (C.C.P.A. 1944). Although *In re Vickers* was a mechanical case, its reasoning applies here. If an inventor had to describe more than what he conceives is his best mode, most patents would be worth little. "The principle of the invention is a unit, and invariable;

the modes of its embodiment in a concrete invention may be numerous and in appearance very different from each other." *Id.* at 991 (quoting *Continental Bag Co. v. Eastern Paper Bag Co.*, 210 U.S. 405, 418 (1908)) (internal quotation marks omitted). Here, as explained above, the principal of the process was operative linkage—overcoming the natural restriction of the cell from making EPO by placing a strong promoter upstream of the EPO gene to be expressed and splicing out the intervening deleterious ATGs. Example 7 describes the best mode—the best process—and should not limit Amgen's right to exclude other processes that fall within the principal of the invention:

> The exclusive right to the thing patented is not secured, if the public are at liberty to make substantial copies of it, varying its form or proportions. And, therefore, the patentee, having described his invention, and shown its principles, and claimed it in that form which most perfectly embodies it, is, in contemplation of law, deemed to claim every form in which his invention may be copied, unless he manifests an intention to disclaim some of those forms.

In re Kirschbraun, 44 F.2d 675, 677 (C.C.P.A. 1930) (quoting *Winans* v. *Denmead*, 56 U.S. (15 How.) 330, 343 (1853)) (internal quotation marks omitted). Thus, Amgen's admission that Dr. Lin had not attempted to place the promoter further upstream is not dispositive. It does not show by clear and convincing evidence that the specification does not reasonable convey that the patentee was in possession but only that Dr. Lodish believed that Dr. Lin had not actually attempted one mode of the invention. Indeed, "patent law permits inventors to obtain patents based entirely on a written description of the invention, without actually constructing or selling the products embodying the invention." Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575, 1681 n.69 (2003).

Moreover, this admission can be distinguished from the admission in *Gentry Gallery, Inc.* v. *Berkline Corp.*, upon which HMR/TKT relies for support. There, Gentry admitted he broadened his claims to cover placement of the controls outside the console only after competitors engaged in such placement. *Gentry*, 134 F.3d at 1479; *see also Amgen II*, 314 F.3d at 1334 (distinguishing the facts in *Gentry).* Further, in *Gentry*, the exact placement of the controls was clearly identified in the specification to be an essential element of the invention. *Gentry*, 134 F.3d at 1479. Here, there is absolutely no indication in the claims or the specification of a locational restriction. So while Dr. Lodish may have admitted that Amgen was not in literal possession of this embodiment of the invention at the time of filing, given the broadness of claims, this admission is not determinative. Judge Miller, as he did dissenting in *Application of Edwards*, would no doubt argue that this is in essence an admission that Amgen was not literally in possession of the invention as claimed since it did not ever even try to move the promoter further upstream. *See Edwards*, 568 F.2d at 1354-55. This Court concludes, however, that although the question is extremely close, Amgen was in possession of the invention as claimed, i.e., it used the words "operatively linked." The specification adequately describes what is claimed—a broad claim. A persuasive analogy is found in the enablement context. There, "[i]t is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention." *Amgen Inc.* v. *Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) [hereinafter *Chugai*] (citing *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976)), and *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) (discussing enablement of a publication under § 102 (b))).

Here, according to undisputed expert testimony, the specification communicates that in order to achieve "operative link[age]," what is important is placing a strong promoter

upstream of the ATG initiating codon of the EPO gene and splicing out unwanted ATGs. One skilled in the art who read Amgen's specification would understand that it is unimportant where upstream the promoter is pl. :ed, so long as it is genuinely "operatively linked." *Cf. Rasmussen*, 650 F.2d at 1214-15 (concluding that the generic step of "adheringly applying" one layer to an adjacent layer satisfied the written description requirement, because "one skilled in the art who read [the] specification would understand that it is unimportant how the layers are adhered, so long as they are adhered."); *Gentry*, 134 F.3d at 1480 (applying *Rasmussen* and considering what one skilled in the art would understand was important or essential to the invention). Amgen may claim other patentable means of operative linkage despite not having provided specific examples in its specification or a boilerplate statement that the examples in the specification were not meant to limit the breadth of the claims. *Rasmussen*, 650 F.2d at 1215; *cf. Kiruschbraun*, 44 F.2d at 677.[89] Thus, the phrase "operatively linked" appears to be supported by the specification.

In a nutshell, HMR/TKT misconstrues the focus of the section 112 inquiry, to wit, whether the claimed subject matter is adequately described, *see, e.g., Ralston-Purina Co.* v. *Far-Mar Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985); *In re Wilder*, 736 F.2d 1516, 1520 (Fed. Cir. 1984), and whether

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[89] HMR/TKT also relies on *PIN/NIP, Inc.* v. *Platte Chemical Co.*, 304 F.3d 1235 (Fed. Cir. 2002), to support its argument. *See, e.g.*, HMR/TKT's Opening Br. After Trial at 48. The situation here, however, is distinguishable. In *PIN/NIP*, the Federal Circuit concluded that the broadened claims incorporated steps that were "quite distinct" from the original claims and what was actually described in the specification. 304 F.3d at 1247-48. None of the methods described in the specification were the same as the method in the broadened claim. *Id.* Here, as discussed above, the methods are the same and further upstream placement of the promoter is not directed to new subject matter different from that described in the patent.

the applicant asserted that he invented that which he did not, *Moba, B.V.* v. *Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003). If the claims contained a limitation regarding promoter placement, HMR/TKT's arguments would have merit. They do not, and HMR/TKT points to nothing in the specification or prosecution history that justifies a location restriction for the promoter. Moreover, the specification adequately describes operative linkage and upstream promoter placement. Thus, HMR/TKT has failed to present clear and convincing evidence that Amgen failed adequately to describe the *claimed* inventions of the '698 and '349 patents.

b. Conclusion

Accordingly, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that the asserted claims of the '698 patent and claim 7 of the '349 patent are invalid for lack of written description under 35 U.S.C. § 112, ¶ 1.

C. Enablement

1. The '698 and '349 Patents

a. Discussion

A patent application must "contain a written description of the invention, and of the manner and process of making and using it . . . as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the same." 35 U.S.C. § 112, ¶ 1 (2000). "To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc.* v. *Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1461 (Fed. Cir. 1993)); *Plant Genetic Systems, H.V.* v. *Dekalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003) (same). The scope of the

claims must reasonably correlate to the scope of enablement provided by the specification to skilled artisans at the time of the patent's effective filing date. *Plant Genetic Systems*, 315 F.3d at 1340; *Hogan*, 559 F.2d at 604 (stating that enablement is determined as of the effective filing date of the patent). Therefore, crucial to the analysis is the state of the art at the time of the application—which is undisputedly 1983-84.

The parties' arguments for non-enablement run parallel to those regarding written description. Although the enablement requirement is separate and distinct from the written description requirement, the written description requirement is broader than the enablement requirement. *Vas-Cath*, 935 F.2d at 1563. Because the Court already held that the asserted claims of the '698 and '349 patents met the written description requirement based on the same arguments and evidence, it need address the enablement issue only briefly.

(1) HMR/TKT's First Argument: Endogenous DNA and Homologuous Recombination

HMR/TKT rightly claims that under the Court's claim construction, the asserted process claims of the '698 and '349 patents "do not enable one of skill in the art to produce EPO from vertebrate cells other than those transfected with exogenous cloned EPO DNA." HMR/TKT's Opening Br. After Trial at 48. As discussed above, however, it is undisputed that in 1983-84, endogenous activation technology and homologous recombination were not known to skilled artisans. HMR/TKT's Findings of Fact ¶ 488; Amgen's Reply to HMR/TKT's Opening Br. After Trial at 34-35. As with the written description requirement, when considering enablement, later states of art cannot be employed as a basis for rejection. *Hogan*, 559 F.2d at 606; *Plant Genetics Systems*, 315 F.3d at 1340 (stating that *Hogan* held that "one could not use later-existing states of the art to invalidate a patent that was enabled for what it claimed at the time of filing"). Thus,

this argument fails with respect to the '349 and '698 patents. Moreover, because HMR/TKT makes no other enablement arguments with respect to claim 7 of the '349 patent, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that Claim 7 of the '349 patent was not enabled.

(2) HMR/TKT's Second Argument: Placement of the Promoter

HMR/TKT argues that Amgen's specification only enables operative linkage of promoter DNA and EPO DNA near or adjacent to the ATG initiation codon of a cloned and isolated EPO gene and that skilled artisans at the time would not have expected promoters placed further upstream to produce EPO. Furthermore, HMR/TKT contends that Amgen's argument—that enablement of one way to make a claimed product suffices—does not apply, because these are process claims not product claims. As a result, HMR/TKT argues, Amgen has forfeited its patent under 35 U.S.C. § 112, ¶ 1 by claiming all processes for making EPO but enabling only one.

HMR/TKT cites no cases that actually support its contention that process claims are somehow different than product claims when it comes to the enablement inquiry. HMR/TKT's Opening Br. After Trial at 49-50. The two cases that HMR/TKT does cite, *Genentech*, 108 F.3d at 1365[90] and *Enzo*

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[90] In *Genentech*, the patentee was "attempting to bootstrap a vague statement of a problem into an enabling disclosure sufficient to dominate someone else's solution of the problem." *Genentech*, 108 F.3d at 1365. This is not the case here. Amgen's specification does not provide "vague intimations of general ideas that may or may not be workable." *Id.* Instead, it provides guidance as to how operatively to link a promoter to EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA. It then provides an example of how this can be done. Moving the location of the promoter further upstream, as discussed above, requires the same methods disclosed in the specification along with an understanding of what actually existed further upstream.

Biochem, Inc. v. *Calgene, Inc.*, 188 F.3d 1362, 1371, 1374-75 (Fed. Cir. 1999),[91] stand only for the unremarkable proposition that a patent must teach those skilled in the art how to make and use the full scope of the invention. The Court holds that the '698 patent meets this requirement.

Here, HMR/TKT has not proved that the disclosure fails adequately to guide the skilled artisan to a process that places the promoter further upstream without undue experimentation. The thrust of HMR/TKT's argument—that the skilled worker would not have expected promoter linkages further upstream to produce EPO—has already been rejected by the Court. As discussed in the written description analysis, this Court finds as a factual matter that skilled artisans at the time of the application filing were aware of how to place promoters further upstream than is shown in example 7 of the '698 patent specification. Moreover, this Court found that all the techniques required to achieve such placement were taught in the specification. According to Dr. Lodish, using the specification, one skilled in the art could have placed a promoter further upstream and produced EPO. While he admitted that some problems might have occurred and that it would have taken a little bit of work, Lodish Test., Trial Tr. at 258, this does not necessarily equate to undue experimentation. *See In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That *some* experimentation may be required is not fatal; the issue

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This, according to Dr. Lodish and undisputed by HMR/TKT, could have been done in 1983-84 with a little bit of work, but was not done, because there was no reason to do it; that is, it would not have increased expression levels significantly.

[91] In *Enzo*, the Federal Circuit declared that the minimal disclosure constituted "no more than a plan or invitation to practice" the invention in cells other than E. coli. *Enzo*, 188 F.3d at 1374. Here, as will be discussed, Amgen provided reasonable detail to enable members of the public to understand and carry out the full scope of the invention without undue experimentation.

is whether the amount of experimentation required is 'undue.'" (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988))); *see also Wands*, 858 F.2d at 737 ("The key word is 'undue,' not 'experimentation.'" (quoting *Angstadt*, 537 F.2d at 504) (internal quotation marks omitted)). Thus, the evidence shows that all the methods required to conduct the process with the promoter further upstream were disclosed and one skilled in the art could replicate the invention using a further upstream promoter placement with some experimentation.

Tellingly, HMR/TKT has neither addressed in its memorandum nor pointed to record evidence regarding the amount of experimentation required by one of skill in the art to use the specification to place the promoter further upstream. Rather, it implicitly asks the Court to infer undue experimentation from general testimony about the development of the technology, the admission that Dr. Lin had not actually tried to place the promoter further upstream and did not know what was upstream of the EPO gene, and the absence of working examples disclosing placement of the promoter further upstream.[92] Given this lack of specific evidence, HMR/ TKT simply has not met its burden to prove undue experimentation. *See Moba*, 325 F.3d at 1321 (reaching a similar conclusion in the absence of specific evidence). First, the Court

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[92] HMR/TKT asserts in its Opening Brief after Trial that the reason that the skilled worker would not have expected that linkages further upstream would produce EPO is that "the expression process would be interrupted or misdirected by sequences, such as other start codons or stop codons, that intervened between the promoter and the EPO DNA." While this information about the difficulties of upstream promoter placement might work to support a finding of undue experimentation, HMR/TKT does not even argue that this is what it shows. Moreover, the only support it provides for this statement is the Court's previous finding in *Amgen I*, which was implicitly rejected by the Federal Circuit. Tellingly, HMR/TKT offers no concrete evidence or expert testimony addressing how it would have been difficult for the skilled artisan to make and use the invention as it is claimed or what type of experimentation would be necessary. *Id.* at 49.

points out that "it is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one of skill in the art to carry out the invention commensurate with the scope of his claims." *Chugai*, 927 F.2d at 1213 (citing *Angstadt*, 537 F.2d at 502); *Donohue*, 766 F.2d at 533 (discussing enablement of a publication under section 102(b) and concluding that "it is not . . . necessary that an invention disclosed . . . have actually been made in order to satisfy the enablement requirement[;] . . . the fact that [the inventor] did not attempt to make his disclosed invention does not indicate one way or the other whether the [patent] [is] enabling"). Second, the evidence produced at trial about the state of the art and the amount of guidance the specification provides suggest the contrary—that the patents at issue do teach those skilled in the art how to make and use the full scope of the invention. *Cf. Wands*, 858 F.2d at 737 (noting that the determination is not a "simple factual determination, but rather is a conclusion reached by weighing many factual considerations"). In light of the presumption of validity, HMR/TKT has failed to carry its burden with respect to this issue.

b. Conclusion

Accordingly, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that the process claims of the '349 and '698 patents were not enabled.

V. INFRINGEMENT

A. The '698 Patent: Claim 4-9

1. Background

At the close of Amgen's case-in-chief in the first trial, and before HMR/TKT had presented its case, this Court granted HMR/TKT's motions for judgments of non-infringement under Fed. R. Civ. P. 52(c), both literally and under the doctrine of equivalents of claims 4-9 of the '698 patent. *Amgen I*,

126 F. Supp. 2d at 99-101. In reaching this decision, the Court compared HMR/TKT's process to the specific embodiments exemplified in the '698 patent and found two significant differences between HMR/TKT's process and Amgen's process: (1) HMR/TKT's process uses homologous recombination to make its erythropoietin-producing cells and HRM/TKT's human EPO gene is endogenous to the human cell, whereas the preferred embodiment of the '698 patent employs heterologous recombination and uses human EPO DNA material that is exogenous; and (2) HMR/TKT's process uses cells in which the CMV promoter and enhancer are placed at a greater distance from the EPO DNA than did the particular examples found in the '698 patent, resulting in several ATG sites in HMR/TKT's process as opposed to only one in Amgen's examples. *Amgen I*, 126 F. Supp. 2d at 102-04. The Court considered these differences to be substantial ones and therefore held that Amgen had failed to show by a preponderance of the evidence that HMR/TKT's process infringes (literally or equivalently) the independent claims of the '698 patent. *Id.*

On appeal, the Federal Circuit vacated and remanded this Court's ruling regarding infringement of the '698 patent because the Court had erroneously compared the accused device to the preferred or commercial embodiments of the patent instead of to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1347. In the course of its ruling, the Federal Circuit made some specific statements about whether this Court's factual findings ought have any bearing on the infringement analysis when properly conducted. With regard to the Court's finding that HMR/TKT's process is homologous, the Federal Circuit pointed out that none of the claims at issue in the '698 patent contains any limitation regarding heterologous recombination. *Id.* Furthermore, the Federal Circuit pointed out this Court's claim construction—as opposed to a specific example in the specification—indicated that

HMR/TKT did infringe the "operatively linked" limitation in the claims.

As discussed briefly in the procedural history portion of this memorandum and order, the Court denied both Amgen's and HMR/TKT's renewed motions for summary judgment regarding infringement of the '698 patent [Doc. Nos. 664 and 665]. As a result, HMR/TKT presented its case on these issues at the remand trial.

HMR/TKT was also allowed to present its defense that it does not literally infringe claims 4-9 of the '698 patent under the reverse doctrine of equivalents. The Court decided to entertain such an argument because the facts that form the reverse doctrine of equivalents defense were always a part of HMR/TKT's interrogatory responses. In *Wright Medical Technology, Inc* v. *Osteonics Corp.*, 122 F.3d 1440, 1445 (Fed. Cir. 1997), the Federal Circuit remanded a case to the district court so it could determine the doctrine of equivalents issue even though the patentee had not argued equivalents, on the basis that the patentee had already introduced evidence in support of this argument. The analysis in *Wright*, although it addresses the doctrine of equivalents and not the reverse doctrine, is applicable here.[93] Therefore, the Court afforded

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[93] It is true that in *Texas Instruments Inc.* v. *United States International Trade Commission*, 988 F.2d 1165, 1176 (Fed. Cir. 1993) ("*Texas Instruments III*") the Federal Circuit refused to consider the alleged infringers' reverse doctrine of equivalents argument because it had not been raised before. *Id.* ("One does not make a reverse doctrine of equivalents argument simply by mounting a defense to literal or doctrine of equivalents infringement."). There, however, the prior proceeding was before the International Trade Commission, which had a strict rule regarding abandonment. In *Rolls-Royce Ltd.* v. *GTE Valeron Corp.*, 800 F.2d 1101, 1108 (Fed. Cir. 1986), however, the court implied that had the alleged infringer at least presented evidence regarding the doctrine of equivalents—even if not the reverse doctrine specifically—it may have entertained the reverse doctrine argument on appeal for the first time. *Id.* (rejecting alleged infringer's reverse doctrine of equivalents argument because there was "no

HMR/TKT the opportunity to present its defense and Amgen the opportunity to rebut.

2. The Claims at Issue

Claims 4 and 6 are the critical claims for resolving the infringement issue, as claims 5, 7, 8, and 9 are dependent.

Claim 4:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

'698 Patent, Ex. 1, col. 38: 37-47 (paragraph structure altered).

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evidence adduced at trial in support of a requested finding that the accused device was so far changed in principle that it performs in a substantially different way"); *cf. Brooktree Corp.* v. *Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1575 (Fed. Cir. 1992) ("[A]n appellate court may, in order to avoid injustice, elect to entertain arguments or consider issues raised for the first time on appeal."). This makes sense given the fact that the reverse doctrine was originally thought to be the application of the doctrine of equivalents in reverse. *See, e.g., Texas Instruments Inc.* v. *United States Int'l Trade Comm'n*, 846 F.2d 1369, 1371 (Fed. Cir. 1988) (*"Texas Instruments II"*) (referring to the reverse doctrine as the "doctrine of non-equivalents"); *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608-609 (1950); *SRI Int'l* v. *Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1124-25 (Fed. Cir. 1985). For more information regarding the genesis of the reverse doctrine of equivalents see overview *infra*. The Court emphasizes that here the procedural posture is different than in these other cases. HMR/TKT here is pursuing this defense at the trial court level, as opposed to the appellate level, and had not presented its full case at the trial court level before the remand trial.

Claim 6:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycoslated erythropoietin polypeptide expressed by said cells.

Id. at col. 38: 50-58 (paragraph structure altered).

3. Literal Infringement

a. Discussion

To determine whether an accused device literally infringes a patent claim, courts apply a two-step analysis. *See, e.g., Watts* v. *XL Sys., Inc.*, 232 F.3d 877, 880 (Fed. Cir. 2000); *Laitram Corp.* v. *Morehouse Indus., Inc.*, 143 F.3d 1456, 1461 (Fed. Cir. 1998). First, the court construes the claims to determine their scope as matter of law. *See Markman*, 517 U.S. at 370. Second, the court determines whether the claims cover the accused device. *See, e.g., Watts*, 232 F.3d at 880; *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc).

The only limitation of claims 4-9 of the '698 patent that HMR/TKT asserts it does not literally infringe is "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." *See, e.g.*, HMR/TKT's Reply Br. After Trial at 26-27; HMR/TKT's Opening Br. After Trial at 10-11. As discussed, *supra*, the Court conducted the first step of the inquiry and construed the term "DNA encoding" to mean "the genetic instructions for" the "mature erythropoietin amino acid sequence of FIG. 6." To conduct the second step, the Court must compare the properly construed claim with the

accused product to determine whether the accused product meets each and every limitation. *Bayer AG* v. *Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247-48 (Fed. Cir. 2000); *Young Dental Mfg. Co.* v. *Q3 Special Prods., Inc.*, 112 F.3d 1137, 1141 (Fed. Cir. 1997).

HMR/TKT argues that the claims require the genetic instructions for an EPO with the fully realized, secreted 166 amino acid sequence of Figure 6. *See* HMR/TKT's Reply Br. After Trial at 26-27; HMR/TKT's Opening Br. After Trial at 10-11. In support it points to the Court's ruling in *Amgen I*, in the context of the '080 patent, that the "mature erythropoietin amino acid sequence of FIG. 6" is "the fully realized form of the amino acid sequence of Figure 6," *Amgen I*, 126 F. Supp. 2d at 100, that is, one with a 166 amino acid sequence.

HMR/TKT's argument fails to persuade the Court because "the mature erythropoietin amino acid sequence of FIG 6" in the context of the '080 patent refers to the structure of the claimed glycoprotein whereas in the '698 claims it refers to the structure of a DNA in the claims.[94] This is not to suggest that the phrase should have different meanings in different contexts. Indeed, the parties agreed in *Amgen I* that the meaning of the term should be the same in both settings. *Amgen I*, 126 F. Supp. 2d at 86. Here, as in the context of the '080 patent, the phrase means the "fully realized form of the amino acid sequence of Figure 6." *Id.* at 87. In the '698 patent, however, the phrase is preceded by "DNA encoding," and thus the primary subject is the DNA whereas in the '080 patent the primary subject is the "erythropoietin glycoprotein" itself. See '080 and '698 Patents, Ex. 1. Although it is true that HMR 4396 is a glycoprotein containing 165 amino acids,

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[94] As Amgen points out (and HMR/TKT does not dispute), "DNA and protein are two distinct types of biological molecules," and, therefore, "the claim limitation must be carefully construed in light of the relevant claim language." Amgen's Reply to HMR/TKT's Findings of Fact at 36.

experts for both parties agree that HMR/TKT's R223 cells contain a DNA encoding EPO that "has the same codons for the same amino acids as is depicted in Dr. Lin's Figure 6." Kingston Test., R. Trial Tr. at 154: 21-155: 15; Lodish Test., Trial Tr. at 245: 16-247: 18; *id.* at 259: 12-15 (stating that HMR/TKT's R223 cells contain amplified DNA encoding the mature erythropoietin amino acid sequence of Figure 6); Lodish Test., R. Trial Tr. at 1066: 23-1067: 18.[95] In other words, each process encodes or provides the genetic instructions for the 1-166 amino acid sequence depicted in Figure 6, as each contains a DNA sequence having codons for amino acids +1 through +166 as depicted in Figure 6. As discussed in *Amgen I*, the reason that HMR/TKT claims an end-product that only has 165-amino acids while Amgen claims one that has 166 is that at the time Amgen's patents were written, it was not yet known that the last amino acid residue ultimately cleaves off prior to secretion of the EPO from the cell. *Amgen I*, 126 F. Supp. 2d at 86, 101.

HMR/TKT argues that "Amgen ignores that the 'cDNA' sequence it relies upon has a 'methionine, alanine, threonine' amino acid sequence, which is exon 1" and is derived from human growth hormone, not from EPO. HMR/TKT's Findings of Fact After Trial at 24, ¶ 104. This argument, however, is irrelevant. First, as Amgen points out—and HMR/TKT does not dispute—this argument involves the amino acids of

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[95] Dr. Lodish based his opinion on a comparison between the sequence of complementary DNA ("cDNA") made by HMR/TKT's contract manufacturer from the EPO DNA in R223 cells and the codons for amino acids at positions +1 to +166 of Figure 6. Lodish Test., R. Trial Tr. at 1066: 23-1067: 18; Lodish Test., Trial Tr. 245: 16-247: 18. It is undisputed that a cDNA is simply a DNA copy of a messenger RNA. In other words, the DNA is transcribed into an RNA transcript first. Then the RNA transcript is spliced into a messenger RNA. The cDNA is made as a direct DNA copy of the messenger RNA using reverse transcriptase so the sequence of the cDNA will be that of the messenger RNA. Lodish Test., R. Trial Tr. at 1066.

the leader sequence in HMR/TKT's R223 cells, yet the claims do not specifically address the leader sequence. Amgen's Reply to HMR/TKT's Findings of Fact at 36. The Court held, in *Amgen I*, that the mature EPO amino acid sequence of Figure 6 included only 166 amino acids, that is, positions +1 through +166. *Amgen I*, 126 F. Supp. 2d at 86, 100 (noting that Figure 6 depicts the amino acids starting from -27, the signal or leader peptide which is cleaved off, and concluding that in order for HMR 4396 to infringe literally, it "must contain an EPO glycoprotein comprising the fully realized erythropoietin amino acid sequence of Figure 6, which depicts 166 amino acids"). Consistent with this holding, Dr. Lodish testified at the remand trial that the amino acid sequence of the mature EPO in Figure 6 begins at the +1 position and ends at +166. Lodish Test., R. Trial Tr. at 1067: 5-18. Amgen's counsel suggested the same to Dr. Kingston, and he never contradicted this implication. Kingston Test., R. Trial Tr. at 156: 14-23 (agreeing with Amgen's counsel's depiction of Figure 6 as having codons for a leader sequence and then codons for the "mature sequence" beginning at +1). Second, this argument ignores expert testimony proffered by both parties, noted above, that HMR/TKT's R223 contain DNA encoding the mature erythropoietin amino acid sequence of Figure 6, as defined by this Court, regardless of any differences in the leader sequences.

Even so, HMR/TKT argues that proof that its DNA is the same as Amgen's DNA is not enough. It contends that the claims require production of an EPO product with 166 amino acids because "the mature erythropoietin amino acid sequence of Fig. 6" is followed in the claims by a clause which states "said glycosylated erythropoietin polypeptide" is "isolated." HMR/TKT's Opening Br. After Trial at 11.

Based on the language of the claims, including the preambles, the Court rejects this argument and concludes that "the mature erythropoietin amino acid sequence of FIG. 6"

modifies the words "DNA encoding" in the cells grown in step (a)—and does not modify "glycosylatd erythropoietin polypeptide" isolated in step (b). This interpretation is supported by evidence, proffered by Amgen and undisputed by HMR/TKT, that the proper antecedent basis is provided only by use of prior *identical* language in the claim. See Manual of Patent Examining Procedure 2173.05(e) (6th ed. 1997); Amgen's Reply to HMR/TKT's Findings of Fact at 37. Here, "glycosylated erythropoietin polypeptide" is previously found only in the preamble and not in part (a) of the claim.[96] Part (a), although it refers to the "mature erythropoietin amino acid sequence of Fig. 6," concerns the DNA that is doing the encoding—not the EPO itself. Part (b) merely addresses the next step in the process which is the step of isolating. Thus, "said glycosylated erythropoietin polypeptide" refers back to the preamble before steps (a) and (b) are described. This is the only reading that makes grammatical sense. Moreover, it is consistent with how the claims of the '080 patent are read. There, "said erythropoietin glycoprotein" always refers back to the exact identical language at the beginning of the claim and not to the attributes of the glycoprotein itself. '080 Patent, Ex. 1, col. 38: 39-50.

b. Conclusion

In sum, Amgen has shown by a preponderance of the evidence that HMR/TKT's HMR 4396 does indeed literally infringe claims 4-9 of the '698 patent. Before ruling that Amgen prevails on this issue, however, the Court must address HMR/TKT's reverse doctrine of equivalents defense.

[96] HMR/TKT neither claims nor cites to any authority claiming that the antecedent for a claim limitation must be found in the meat of the claim and not in the preamble.

4. Reverse Doctrine of Equivalents

a. Overview of the Doctrine

The reverse doctrine of equivalents is an equitable doctrine that a court applies when it finds that the accused device literally infringes a patented invention, but is so fundamentally different from the patented invention that a judgment of infringement would be inappropriate. *Texas Instruments, Inc.* v. *United States International Trade Commission*, 846 F.2d 1369, 1371 (Fed. Cir. 1988) (*"Texas Instruments II"*) (noting that it might be better described as "the doctrine of non-equivalents"); *Scripps Clinic & Research Found.* v. *Genentech Inc.*, 927 F.2d 1565, 1581 (Fed. Cir. 1991). The doctrine was first articulated by the Supreme Court in *Boyden Power-Brake Co.* v. *Westinghouse*, 170 U.S. 537, 568 (1898) (establishing that the doctrine of equivalents could be used defensively); *Gillette* v. *S.C. Johnson & Son, Inc.*, Nos. 83-2657-N, 83-3201-N, 1989 WL 87374, at *19 (D. Mass. July 31, 1989) (Collings, M.J.) (commenting that *Westinghouse* was the seminal case respecting the reverse doctrine of equivalents); George M. Sirilla, Thomas P. Feddo & Michael C. Antone, *The Doctrine of Equivalents: Both a Sword and a Shield*, 13 Fed. Cir. B.J. 75, 77-78 (2003) (noting that *Westinghouse* was a "seminal case" in establishing the use of the doctrine of equivalents as a shield); John F. Duffy, *The Festo Decision and the Return of the Supreme Court to the Bar of Patents*, 2002 Sup. Ct. Rev. 273, 315 (2002). Approximately fifty years later, in *Graver Tank & Mfg. Co.* v. *Linde Air Products Co.*, 339 U.S. 605, 608-609 (1950), the Supreme Court explicitly endorsed the reverse doctrine of equivalents. *Graver Tank*, 339 U.S. at 608-609 (noting that the doctrine of equivalents "is not always applied in favor of the patentee but is sometimes used against him" when "the invention is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way"); *Scripps*, 927 F.2d at 1581 (quoting *Graver Tank*);

Tate Access Floors, Inc. v. *Interface Architectural Res. Inc.*, 279 F.3d 1357, 1368 (Fed. Cir. 2002) (remarking that the Supreme Court referred to the reverse doctrine in *Graver Tank*).

The reverse doctrine of equivalents is applied equitably based upon factual determinations made after "the accused infringer proves that, despite the asserted claims literally reading on the accused devise, 'it has been so changed that it is no longer the same invention.'" *Amgen II*, 314 F. 3d at 1351 (quoting *Del Mar Avionics, Inc.* v. *Quinton Instrument Co.*, 836 F.2d 1320, 1325 (Fed. Cir. 1987)).[97] As the Supreme Court explained in *Westinghouse:*

> The patentee may bring the defendant within the letter of his claims, but if the latter has so far changed the principle of the device that the claims of the patent, literally construed, have ceased to represent his actual invention, he is as little subject to be adjudged an in-

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[97] The Federal Circuit made clear in *SRI International*, that after the patentee has proved literal infringement, "*the accused infringer* may undertake the burden of going forward to establish the fact of non-infringement under the reverse doctrine of equivalents." 775 F.2d at 1123-24 (emphasis added). It is only *after* the alleged infringer makes a prima facie showing that its process is so far changed in principle from the claimed processes that the patentee, "who retains the burden of persuasion on infringement," must rebut. *Id.* at 1124; *see also SmithKline Diagnostics, Inc.* v. *Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (observing that the infringement inquiry does not necessarily end when claims read literally on the accused product because the accused "may establish the fact of non-infringement by carrying its burden of going forward to show its device 'has been so far changed in principle that it performs the same or similar function in a substantially different way'" (quoting *SRI International*, 775 F.2d at 1123-24)).

Thus, here—notwithstanding its unpersuasive arguments to the contrary—HMR/TKT has the burden of making a prima facie showing that "the accused device is outside the fair and equitable scope of the invention." Sirilla, Feddo & Antone, *supra*, at 101.

> fringer as one who has violated the letter of a statute has to be convicted, when he has done nothing in conflict with its spirit and intent.

170 U.S. at 568. Thus, the determination of whether the reverse doctrine should apply is not made in a vacuum. *Graver Tank*, 339 U.S. at 609; *Amgen II*, 314 F.3d at 1351. Nor is it made by merely considering the language of the claims themselves.[98]

Rather, the Court must determine the originally intended scope, the "spirit and intent" of the claims, *Westinghouse*, 170 U.S. at 568, based on the "the context of the patent, the prior art, and the particular circumstances of the case." *Graver Tank*, 339 U.S. at 609; *see also Texas Instruments II*, 846 F.2d at 1372 (explaining that the reverse doctrine concerns the "original intended scope" of the claims); *Scripps*, 927 F.2d at 1581 ("[T]he purpose of the 'reverse' doctrine is to prevent unwarranted extension of the claims beyond a *fair* scope of the patentee's invention." (emphasis added)). In other words, "the analysis requires a determination of the 'substance of the invention,' the 'thing' or 'article' patented, or 'the principle of the device.'" Sirilla, Feddo & Antone, *supra*, at 83 (citing *Festo II*, 535 U.S. at 731, *Westinghouse*, 170 U.S. at 568, and *Winans*, 56 U.S. at 343).

Although the Federal Circuit recognizes this doctrine, it is rarely invoked successfully. Shyh-Jen Wang & Shyh-Yau Wang, *The Verification Flow Chart of Patent Infringement*, 86 J. Pat. & Trademark Off. Soc'y 74, 78 (2004) ("[I]t is not often raised and even less frequently successful."); Burk & Lemley, *supra*, at 1657. Indeed, according to the Federal Circuit, it has never upheld a decision of non-infringement based on the reverse doctrine of equivalents. *Tate*, 279 F.3d at

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[98] If it were based solely on the claim language itself, the analysis would not differ from basic literal infringement and section 112 analysis.

1368 (labeling the reverse doctrine "anachronistic").[99] This may be because circumstances in which the doctrine is satisfied are very rare. *See, e.g., SRI Int'l*, 775 F.2d at 1124, n.19 ("Because products on which patent claims are readable word for word often are in fact the same, perform the same function in the same way, and achieve the same result, as the claimed invention, a defense based on the reverse doctrine of equivalents is rarely offered."); *Caterpillar Tractor Co.* v. *Berco, S.P.A.*, 714 F.2d 1110, 1115, n.3 (Fed. Cir. 1983) ("It is possible, of course, for a claim to be literally but not actually infringed, where, for example, a claim may 'read on' a structure having no relation to the invention. Instances are rare."); Donald S. Chisum, *Chisum on Patents*, § 18.04 (4) (b) at 18-392 (2000).[100] On the other hand, its rarity may be, as the

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[99] Although the Federal Circuit may never have upheld a decision based on the reverse doctrine of equivalents, some appellate courts, before the Federal Circuit was created, applied the doctrine of equivalents defensively without expressly identifying it as the reverse doctrine. *See, e.g., Leesona Corp.* v. *United States*, 530 F.2d 896, 906 (Ct. Cl. 1986); *Foster Cathead Co.* v. *Hasha*, 382 F.2d 761, 765 (5th Cir. 1967); *see also* Sirilla, Feddo & Antone, *supra*, at 86-87 (commenting on these decisions and concluding that each implicitly applied the reverse doctrine of equivalents).

[100] District Courts also appear to be reluctant to apply the reverse doctrine of equivalents. *But see Marvin Glass & Assocs.* v. *Sears, Roebuck & Co.*, 318 F. Supp. 1089, 1104-5 (S.D. Tex. 1970). Although the reverse doctrine is recognized, it is often deemed inapplicable, or the court finds that there is insufficient evidence to support application of the doctrine. *See, e.g., SDS USA Inc.* v. *Ken Specialties, Inc.*, 122 F. Supp. 2d 533, 541 (D. N.J. 2000); *cf. Monsanto Co.* v. *Mycogen Plant Science, Inc.*, 61 F. Supp. 2d 133, 188 (D. Del. 1999) (entering judgement as matter of law, holding that the jury acted unreasonably in finding non-infringement based on reverse doctrine of equivalents). There are instances, however, where district courts have based a finding of non-infringement on the reverse doctrine of equivalents or used it as an alternative ground for their decision. *See, e.g., Precision Metal Fabricators* v. *Jetstream Sys.*, 693 F. Supp. 814, 819 (N.D. Cal. 1988) (granting summary judgment in favor of defendants based on the reverse doctrine of equivalents); *Brenner* v. *Rec-*

Federal Circuit suggested in *Tate*, a result of the enactment of 35 U.S.C. § 112. *Tate*, 279 F.3d at 1368 (explaining that "the written description requirements of 35 U.S.C. § 112 are co-extensive with the broadest possible reach of the reverse doctrine of equivalents"); Joseph Yang & Roxana H. Yang, *An Update on the Doctrine of Equivalents—Where Do We Stand in 2003?*, 749 Practicing L. Inst. 521, 561 (2003) (concluding that this is a dead doctrine due to the enactment of section 112). In other words, alleged infringers that perhaps could successfully have evoked the reverse doctrine of equivalents do not attempt to do so because they prevail with section 112 challenges on grounds such as inadequate written description, lack of enablement, or means-plus-function. *See, e.g.*, *Texas Instruments, Inc.* v. *United States Int'l Trade Comm'n*, 805 F.2d 1558, 1571-2 (Fed. Cir. 1986) ("*Texas Instruments I*") (applying the principles underlying the reverse doctrine of equivalents in the context of section 112, paragraph 6). As the Federal Circuit explained in *Texas Instruments II*, 846 F.2d at 1372, section 112 and the reverse doctrine are intertwined:

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ognition Equip. Inc., 593 F. Supp. 1275, 1278 (S.D.N.Y. 1984) (invoking the reverse doctrine of equivalents as an alternative ground for non-infringement); *SmithKline Diagnostics, Inc.* v. *Helena Labs., Inc.*, 662 F. Supp. 622, 628 (E.D. Tex. 1987) (same); *Technicon Instruments Corp.* v. *Alpkem Corp.*, 664 F. Supp. 1558, 1575 (D. Or. 1986). It appears, however, that the District Court of Massachusetts has never held non-infringement based on the reverse doctrine of equivalents. *VLT, Inc.* v. *Power-One, Inc.*, No. 01-CV-10207, 2003 WL 43364 (D. Mass. Jan. 3, 2003) (Saris, J.) (concluding that the court need not address the reverse doctrine of equivalents because the court rejected the proposed claim construction); *Amgen, Inc.* v. *Chugai Pharmaceuticals Co., Ltd.*, Civ.A. No. 87-2617-Y, 1989 WL 169006, at *85 (D. Mass., Dec. 11, 1989) (Saris, J.) (explaining that defendants should request reconsideration by this Court if they want to raise the issue); *Gillette* v. *S.C. Johnson & Son, Inc.*, Nos. 83-2657-N, 83-3201-N, 1989 WL 87374, at *19 (D. Mass. July 31, 1989) (Collings, M.J.).

> The reverse doctrine of equivalents is invoked when claims are written more broadly than the disclosure warrants. The purpose of restricting the scope of such claims is not only to avoid a holding of infringement when a court deems it appropriate, but often is to preserve the validity of the claims with respect to their original intended scope.

846 F.2d 1369, 1372.[101]

Despite the paucity of cases relying on the reverse doctrine, the doctrine is not yet dead.[102] Indeed, just last year, the Federal Circuit implied in two separate cases that the reverse doctrine of equivalents still had a heart beat, albeit a faint one. *See Amgen II*, 314 F.3d at 1351 (discussing the doctrine as though it were a viable one, but holding that it did not apply to the case at bar); *Plant Genetic Systems, N.V.* v. *Dekalb Genetics Corp.*, 315 F.3d 1335, 1341 (Fed. Cir. 2003) ("[T]he judicially-developed 'reverse doctrine of equivalents,' requiring interpretation of claims in light of the specification, may be safely relied upon to preclude *improper* enforcement against later developers."); Burk & Lemley, *supra*, at 1657, n.308 (interpreting *Amgen II* as implying the viability of the reverse doctrine). This is rightly so.

Although both the reverse doctrine of equivalents and section 112 spring from the same roots and very often take

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[101] If the claims are broader than the "spirit and intent" of the invention, this will most likely be apparent by a close reading of the specification. At this point, a section 112 challenge may be initiated in lieu of a reverse doctrine of equivalents argument. As discussed immediately *infra*, however, this challenge may not always be successful. This is where the reverse doctrine of equivalents comes in.

[102] Despite not relying on it, the Federal Circuit has affirmed the viability of the reverse doctrine of equivalents many times, *see, e.g.*, Sirilla, Feddo & Antone, *supra*, at 87-97 and app. A (identifying many cases that applied the principals of the reverse doctrine and that supported its viability).

account of the same factors and considerations," *Texas Instruments II*, 846 F.2d at 1372 (Davis, J., concurring),[103] the reverse doctrine is theoretically—if not practically—distinct from section 112 requirements. *See, e.g.*, *Warner-Jenkinson Co, Inc.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17, 35 (1997) (rejecting the notion expressed in *Tate* that section 112 nullified or codified the reverse doctrine); *cf.* Sirilla, Feddo & Antone, *supra*, at 82, 102 (stating that the requirements of section 112 provide the context in deciding the rightful reach of the claims and thereby implying that section 112 and the reverse doctrine are distinct); Ronald D. Hantman, *Why Not the Statute?: Revisited*, 83 J. Pat. & Trademark Off. Soc'y 685, 704 (2001) (noting that "the Federal Circuit has interpreted the reverse doctrine of equivalents as distinct from section 112" but opining that they are not). The reverse doctrine of equivalents, unlike the requirements of section 112, supports innovation—especially in the area of biotechnology where blocking patents are common—because it offers some chance of protection to those that make substantial changes or radical improvements to inventions. Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 Tex. L. Rev. 989, 991, 1011, 1067 (1997) ("*Economics*") ("The application of the reverse doctrine is to protect substantial improvers from infringing if they are sufficiently radical."); *cf.* Burk & Lemley, *supra*, at 1681; Mark R. Patterson, *Inventions, Industry Standards, and Intellectual Property*, 17 Berkeley Tech. L.J. 1043, 1052 (2002) ("The reverse doctrine of equivalents can be viewed as a means of

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[103] Indeed, many scholars and judges have noted the similarity in operation between applying section 112, ¶ 6 and the reverse doctrine of equivalents. Both restrict the coverage of literal claim language. *See, e.g.*, *Valmont* v. *Reinke*, 983 F.2d 1039, 1042 (Fed. Cir. 1993); *Johnston* v. *IVAC Corp.*, 885 F.2d 1574, 1580 (Fed. Cir. 1989); *see generally* Gary M. Butter, Marta E. Delsignore, Kimberly J. McGraw & Louis S. Sorell, *Selected Aspects of the Impact of Patent Prosecution on Patent Litigation Issues*, 750 Practicing L. Inst. 317 (2003).

avoiding hold-ups that can deter innovation."); *see also* Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 Colum. L. Rev. 839, 866 (1990) ("[T]he reverse doctrine of equivalents solves the problem of [hold-up by blocking patents] by, in effect, excusing the improver from infringement liability—and therefore removing the original patentee's hold-up right.").[104] As the Federal Circuit explained in *Plant Genetics*, should an alleged infringer lose its section 112 arguments because the technology was new and therefore did not need to be described or enabled, it can bring a challenge under the reverse doctrine of equivalents. *Plant Genetics*, 315 F.3d at 1341. Thus, the reverse doctrine, unlike section 112, acts as a "judicial safety valve," Robert Merges, *Intellectual Property Rights and Bargaining Breakdown: The Case of Blocking Patents*, 62 Tenn. L. Rev. 75, 75-76 (1994) ("*Blocking Patents*"), allowing consideration of equity and fairness, "soft factors," that a section 112 inquiry does not incorporate.[105] In essence, the reverse doctrine, when equity demands it, re-verses the protection given to broad patents that satisfy section 112. *Cf.* Lemley, *Economics*, at 1003 (noting that patent owners are not limited to what they actually discovered "so long as the

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[104] A blocking patent situation occurs when an improvement is patented but the improvement patent infringes on the original patent. Lemley, *Economics*, at 1009-1010. The original patent owner is entitled to damages from past infringement and an injunction against future use of the infringing invention. *Id.* At the same time, however, the original patent owner cannot use the patented improvement without risking liability for damages and a potential injunction. *Id.* Thus, "the original patent owner can prevent the improver from using his patented technology but the improver can prevent the original patent owner from using the improvement. Unless the parties bargain, no one gets the benefit of the improvement." *Id.*

[105] Merges argues that it should be used by judges to "releas[e] pressure that builds up when pioneers and improvers fail to agree to a license." Merges, *Blocking Patents*, at 75-76.

patentee describes the general class and its characteristics with sufficient precision that others can identify and use them without undue experimentation"); *cf.* Antony L. Ryan & Roger G. Brooks, *Innovation vs. Evasion: Clarifying Patent Rights in Second Generation Genes and Proteins*, 17 Berkeley Tech. L.J. 1265, 1280 (2002) (noting that "in theory the reverse doctrine of equivalents" could provide some relief in the biotech arena where innovation is stifled by broad patents but concluding that it is applied so rarely that its comfort is slight); Toshiko Takenaka, *Doctrine of Equivalents After* Hilton *Davis: A Comparative Law Analysis*, 22 Rutgers Computer & Tech. L.J. 479, 506-07 (1996) ("Application of the reverse doctrine of equivalents may prevent enforcing the patent as broadly as drafted.").

This is not to suggest that the reverse doctrine of equivalents should be invoked frequently. To the contrary, it should be saved—and apparently is—for the inventor that *radically*, not just modestly, improves upon the prior art such that there is a "manifest departure from the principle in the [patentee's] patent." *Westinghouse*, 170 U.S. at 572, 579 (commenting that the alleged infringer's invention did not infringe not just because it was novel or changed in principle but because it solved an important problem that the patentee's invention did not and pointing out that the alleged infringer's invention was a "radical departure");[106] *see generally SRI International*, 775 F.2d at 1123 (emphasizing that the reverse doctrine protects when the alleged infringer's device is "so *far* changed in principle that it performs in a *substantially different* way"

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[106] In *Westinghouse*, the device described by the original patentee could not produce the result achieved by the accused device, that is, it could not quickly and smoothly stop a moving train. *Westinghouse*, 170 U.S. at 571-72. The Supreme Court held that the alleged infringer's way of accomplishing the function of the patent, applying brakes to a moving train, was such a "radical departure," *id.* at 579, and "so different" that infringement could not be found. *Id.* at 723-24.

(internal quotation marks omitted)); *Scripps*, 927 F.2d at 1581 (suggesting application of the reverse doctrine on remand where the defendant produced similar biological materials by a potentially radically new biotechnological process); *cf. Winans*, 56 U.S. at 342-343 ("It is only *ingenious* diversities of form and proportion, presenting the appearance of something unlike the thing patented," which indicate that infringement should not be found. (emphasis added)); *see also Diamond Int'l Corp.* v. *Maryland Fresh Eggs, Inc.*, 374 F. Supp. 1223, 1247 (D. Md. 1974) (noting that it is the "really meritorious improver" who deserves the benefit of the concept of the reverse doctrine of equivalents), *rev'd on other grounds*, 523 F.2d 113 (4th Cir.); Lemley, *Economics*, at 1067; Merges, *Blocking Patents*, at 92-94 (opining that the alleged infringer must show a "radical improvement" or "significant contribution" or "substantial technological improvement" such as that shown in *Westinghouse* or *Scripps*); Donna M. Gitter, *International Conflicts Over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, 76 N.Y.U. L.R. 1623, n.411 (2001); Sean Hogle, *Unauthorized Derivative Source Code*, 18 No. 5 Computer & Internet Law. 1, 3 (2001). Only then will the certainty of patent law be preserved while still encouraging and rewarding substantial, radical, innovation. Merges & Nelson, *supra*, at 867 n.120; *cf.* Merges, *Blocking Patents*, at 92 (asserting that the reverse doctrine creates enough of a threat to pioneer patentees to positively influence the changes of a society productive agreement between the pioneer and radical improver); Lemley, *Economics*, at 1012 ("The reverse doctrine of equivalents therefore benefits radical improvers at the expense of the original patentee, and so encourages radical improvements, just as the blocking patents rule provides some lesser encouragement to significant improvements.").

b. Discussion

HMR/TKT argues that it does not infringe claims 4-9 of the '698 patent because its process is "so far removed in terms of its principles of operation from the process Amgen disclosed." HMR/TKT's Opening Br. After Trial at 18. Although HMR/TKT proffers many reasons in support of its position, it has failed to make out a prima facie case.[107] As Amgen aptly points out, HMR/TKT makes the same mistake with each of its arguments. It repeatedly compares its process to the examples disclosed in Amgen's patent specification instead of to the "equitable scope of the claims." *Scripps*, 927 F.2d at 1581 ("Application of the doctrine requires that facts specific to the accused device be determined and weighed against the equitable scope of the claims, which in turn is determined in light of the specification, the prosecution history, and the prior art."); *cf. Amgen II*, 314 F.3d at 1351 (rejecting HMR/TKT's reverse doctrine of equivalents arguments regarding the '349 patent that compared its invention to the examples in the specification and not to the claims); *SDS USA, Inc.* v. *Ken Specialties, Inc.*, 122 F. Supp. 2d 533, 541 (D.N.J. 2000) (holding that the accused infringer had "fail[ed] to mount a prima facie case because it [had] compare[d] the accused product not to the . . . patent, but to [the patentee's] commercial embodiment"). The proper question, however, is how any purported differences are changed in principle from Amgen's patented processes given "the context of the patent, the prior art, and the particular circumstances of the case." *Graver Tank*, 339 U.S. at 609; *United States Steel Corp.*, 865 F.2d at 1253 n.9. (affirming district court's decision that was based on the principle of the contribution made by the inventor); *Scripps*, 927 F.2d at 1581. Thus, as will be explained below, although HMR/TKT

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[107] Even if HMR/TKT had made out a prima facie case, Amgen has successfully rebutted the defense, as will be made clear in the discussion below.

presents evidence showing many differences between its process and those specifically exemplified in Amgen's specification, it fails to prove that these differences matter.[108]

(1) Homologous Recombination, Endogenous EPO DNA, and The Neighborhood's Effect on the Production of EPO

(a) Homologous Recombination and Endogenous EPO DNA[109]

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[108] HMR/TKT groups and labels its reasons for applying the reverse doctrine of equivalents differently in its various submissions. *See, e.g.*, HMR/TKT's Opening Br. After Trial 11-19; HMR/TKT's Proposed Findings of Fact at 25-41. For ease of analysis, based on the parties' arguments at trial and submissions after trial, and the overlap among the arguments, the Court groups HMR/TKT's reasons into four areas. While the Court has considered each of HMR/TKT's contentions, and concluded that each fails for the primary reasons explained above, not every contention need be addressed specifically in this section.

[109] The Court first addresses homologous recombination and endogenous EPO DNA because HMR/TKT seems to assert that these points, in their own right—aside from the neighborhood theory—work to justify evocation of the reverse doctrine of equivalents. HMR/TKT's reliance on these differences appears to stem from the Court's prior factual findings and legal conclusions. Indeed, the Court previously found that HMR/TKT did not equivalently infringe the '698 patent because HMR/TKT's process performs the same function in a substantially different way, based, in part, on the fact that HMR used homologous recombination and endogenous EPO DNA while the embodiments in Amgen's specification only addressed heterologous recombination and exogenous EPO DNA. *Amgen I*, 126 F. Supp. 2d at 102-04. As discussed earlier, however, the Federal Circuit held this comparison between HMR/TKT's process and the embodiments in Amgen's specification to be erroneous. *Amgen II*, 314 F.3d at 1347. While it is true that "equivalence and non-equivalence, . . . are but opposites of the same coin," *Sri Int'l*, 775 F.2d at 1124-25, candidly, the Court in *Amgen I* did not conduct the proper equivalents analysis. Moreover, it did not, in making its prior determination, consider the intended scope of the claims or the principles of the invention—key components of any reverse doctrine of equivalents analysis. In short, the Court's prior equivalence determination was not based on the correct or

HMR/TKT repeatedly asserts that (1) its process is different because it uses homologous recombination (as opposed to heterologous recombination); and (2) its EPO gene is different in structure because HMR/TKT's EPO DNA is endogenous and Amgen's is exogenous. HMR/TKT's Opening Br. After Trial at 13; HMR/TKT's Proposed Findings of Fact ¶ 141; HMR/TKT's Reply Br. After Trial at 28.[110]

Tellingly, aside from the neighborhood theory (discussed immediately below), HMR/TKT does not even attempt to explain how these differences matter—that is, how they are different in principle from the processes disclosed in Amgen's patents. Instead, it primarily relies on this Court's prior findings, in the equivalent infringement context, that HMR/TKT's process is not substantially similar to Amgen's because, *inter alia*, it uses homologous recombination and

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complete set of factors upon which a determination regarding equivalents should be made. Therefore, the Court's prior holding that HMR/TKT's process performs the same function in a substantially different way is simply irrelevant to this analysis here.

[110] As discussed earlier, it is undisputed that endogenous activation technology and homologous recombination were unknown to those skilled in the art when Amgen filed its patent application in 1983-84. HMR/TKT's Findings of Fact ¶ 488; Amgen's Reply to HMR/TKT's Opening Br. After Trial [Doc. No. 815] at 34-35. As a result, exogenous EPO DNA expression systems and heterologous recombination techniques were not depicted in Amgen's examples in the patent. Trial Tr. at 375: 19-25; 376-381; *see also Amgen I*, 126 F. Supp. 2d at 102. For example, Amgen's patent describes transfecting Chinese Hamster Ovary ("CHO") cells with a vector that contains both viral promoter DNA and the human EPO gene. '933 Patent, Ex. 1, col. 25: 55-61; Trial Tr. at 174: 18-22, 1330: 2-5. Thus, the human EPO DNA material is exogenous to the hamster host cell. *Id.*; *Amgen I*, 126 F. Supp. 2d at 102. HMR/TKT, on the other hand, employs homologous recombination. *Id.* HMR/TKT does not utilize a host cell from a non-human species; rather, it manipulates the human EPO gene where it naturally resides in an HT1080 human cell line. Trial Tr. at 165: 21. The human EPO gene, therefore, is endogenous to the human cell as opposed to exogenous.

endogenous activation techniques. *See, e.g., Amgen I*, 126 F. Supp. 2d at 102-03 (concluding that "[HMR/]TKT is able to express high levels of human EPO in human cells without having to rely upon host cells from alternative species"). While it is true that the Court in *Amgen I* asserted that use of endogenous DNA was "an important distinction" in its eyes, the Court's vantage point has now changed. The Federal Circuit has made clear that the proper infringement analysis—of which the reverse doctrine of equivalents is a part—requires the Court to look at the properly construed claims and not to limit its purview to the invention as described in embodiments in the specification. *See Amgen II*, 314 F.3d at 1351 (making clear that the claims must frame the analysis when considering the reverse doctrine of equivalents). Clearly, endogenous DNA and homologous recombination are not explicated in any claim limitations. Moreover, the Court has already found—and the Federal Circuit upheld—that the specification does not limit the claims to exogenous activation and homogenous recombination. *Id.* Thus, the mere fact that HMR/TKT utilizes these other techniques does not alone demonstrate any substantial change from Amgen's patents. As the Court found in *Amgen I* in the context of the '349 patent, whether DNA encoding human EPO originated within or outside of the host cell simply does not matter, because the coding sequences of the DNA are the same and both DNA sequences function the same way to produce human EPO. 126 F. Supp. 2d at 121; *see also* Lodish Test., R. Trial Tr. at 1098: 6-12.

True, heterologous recombination and endogenous activation techniques were not known by skilled artisans at the time Amgen filed its application. Equivalent infringement, however, is evaluated based on the date of infringement. *Warner-Jenkinson*, 520 U.S. at 37. Here, the evidence does not show that these techniques are different in principle than those espoused in Amgen's patent. Moreover, the mere use of new technology—even when it is superior—does not on its own

justify the application of the reverse doctrine of equivalents. *Westinghouse*, 170 U.S. at 723 (noting that infringement can be found even if the device is an improvement upon that of the patentee); *Studiengesellschaft Kohle, m.b.H.* v. *Dart Indus., Inc.*, 726 F.2d 724, 728 (Fed. Cir. 1984) ("That [the alleged infringer's] catalysts may be superior to those actually invented, disclosed, and contemplated by [the patentee] would not by itself remove [the alleged infringer's] catalysts from the scope of [the patentee's] claims."); *Phillips Petroleum Co.* v. *United States Steel Corp.*, 673 F. Supp. 1278, 1357 (D. Del. 1987) (similar); Lemley, *Economics*, at 1010-11 (noting that "any invention, no matter how pioneering, can be thought of as an improvement on prior work," and that "not all improvements escape infringement," even significant ones, but that "radical improvements are protected under the reverse doctrine of equivalents"). HMR/TKT must somehow show its product or process is changed "in principle" from what is embraced in the patent claims—that is, that these differences "amount to a significant contribution that takes the invention outside the equitable bounds of the patent." *Westinghouse*, 170 U.S. at 572, 579 (noting that it was not just novel but also a substantial improvement); *cf. Scripps*, 927 F.2d at 1581; Merges & Nelson, *supra*, at 864-65 (interpreting the reverse doctrine as requiring not just novelty but a significant contribution or substantial improvement and relying on *Westinghouse* and *SRI International* as support). Importantly, HMR/TKT provides no support—aside from this Court's dicta—that its endogenous activation technique or homologous recombination was an improvement "so radical that it fundamentally changed the nature of the invention." Lemley, *Economics*, at 1067. HMR/TKT merely points to differences such as "endogenous genes in mammalian cells have a methylation pattern that exogenous genes lack." HMR/TKT's Proposed Findings of Fact ¶ 141. Aside from the neighborhood theory, discussed and rejected by the Court

below, HMR/TKT does not explain how these differences matter. Its showing is simply inadequate.

(b) The Endogenous EPO Neighborhood and Its Effect on EPO Production

HMR/TKT argues that how the gene construct "functions with the surrounding neighborhood to produce EPO is completely different in HMR/TKT's and Amgen's cells." HMR/TKT's Proposed Findings of Fact at 29-32; HMR/TKT's Opening Br. After Trial at 16 (claiming that the way in which expression of human EPO is accomplished is significantly different in HMR/TKT's process). In support, it explains that HMR/TKT activates the normally silent EPO gene and inserts it amidst the endogenous EPO neighborhood. HMR/TKT's Proposed Findings of Fact ¶¶ 122-125. This, according to HMR/TKT, enables the promoter "to work with other nearby enhancers and the EPO gene neighborhood to contribute to the gene's transcriptional activity," *id.* ¶ 124, and to "produce higher levels of EPO," *id.* ¶ 129. *See id.* ¶¶ 126-138.[111]

While this theory is intriguing—and might well have justified invocation of the reverse doctrine of equivalents—the evidence HMR/TKT presented fails sufficiently to support it.

HMR/TKT relied primarily on Dr. Kingston's testimony to elucidate its neighborhood theory. Dr. Kingston testified that the neighborhood around the EPO gene affects expression capability. *See, e.g.*, Kingston Test., R. Trial Tr. at 36. He explained that HMR/TKT uses an endogenous EPO promoter in a region that is normally set up to express EPO. Therefore,

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[111] It is clear that HMR/TKT claims its construct has a more efficient expression system—expressing more EPO per gene copy than the cells made following example 10 in Amgen's patent. *See, e.g.*, HMR/TKT's Reply Br. After Trial at 29-30. It is unclear, however, whether it is truly claiming that its process makes more EPO, as it appears from some of its submissions. Regardless, HMR/TKT never provides any support for such a contention, as will be discussed further below.

like a hotel that is positioned in the heart of the city, he argued, it is helped by its surroundings, that is, the nearby regulatory sites "all work together to help keep this gene on." *See, e.g.*, Kingston Test., R. Trial Tr. at 26-28. This is different, according to Dr. Kingston, than Amgen's process which, as explained in the specification, randomly integrates exogenous DNA, leaving the potential surroundings up to chance. *Id.* at 26-28 ("A gene that has gone into an open region that doesn't happen to be near any other regulatory elements" may have "nothing in its surroundings to help it stay on."); *id.* at 151. Dr. Kingston opined that it was the neighborhood—and not the difference in promoter strength, culture conditions, media, or cell type, or any other factors—that caused HMR/TKT's construct to express more EPO per gene copy than the cells made following example 10 in Amgen's patent. *Id.* at 29-33.

Although this testimony is compelling, it fails to persuade the Court for three reasons. First, notwithstanding Dr. Kingston's testimony to the contrary, the bulk of the credible evidence demonstrates that the endogenous regulatory sequences surrounding the EPO gene in HMR/TKT's construct are "inactive" and actually do not work with the CMV promoter to enhance EPO reproduction in the R223 cells. Dr. Wall testified that the EPO neighborhood in HRM/TKT's cells does not enhance their ability to produce EPO. Wall Test., R. Trial Tr. at 1149: 3-5, 1161-62. Specifically, he explained

> The genomic neighborhood around the EPO gene is there to constrain the expression of the EPO gene in very specific cells; and in all the rest of the cells in the body the genomic neighborhood is silent, it's shut down, it's not responsive to hypoxia. So the genomic neighborhood is not set there to somehow enhance the activity of this really robust viral promoter. Instead, it's there to exqui-

sitely restrict the level and the tissue-specific activity of the EPO gene expression.

Id. at 1161: 18-1162: 2; *id.* at 1148: 13-25, 1149: 5-9, 1162: 15-1163: 11. *See also* Lodish Test., R. Trial Tr. at 1085-86 (disagreeing with Kingston's neighborhood theory). Moreover, contrary evidence exists not merely from Amgen but also from HMR/TKT itself. In its own FDA filings, HMR/TKT admitted that the regulatory sequences surrounding the EPO gene in HMR/TKT's construct are not active and actually are bypassed. HMR/TKT's IND, Ex. 18, at 16 (stating that HMR/TKT's technology works by "bypassing regulatory DNA sequences set in the "off position"); HMR/TKT's IND, Ex. 19, at 561.

Second, Dr. Kingston—the sole exponent of the neighborhood theory—did not perform any experiment to validate his conclusions. Kingston Test., Trial Tr. at 1495: 9-1496: 16; Kingston Test., R. Trial Tr. at 189: 14-16; Lodish Test., R. Trial Tr. at 1086 (noting that there is no evidence that supports Dr. Kingston's contention); *id.* at 1096: 1-5. He merely compared HMR/TKT's R223 cell experiments with Amgen's Example 10 cell experiments. These comparisons do not, on their own, establish Dr. Kingston's conclusions. As both Dr. Lodish and Dr. Wall pointed out—and Dr. Kingston did not dispute—Dr. Kingstown compared EPO production per gene copy by looking at experiments with cells grown in different locations under different conditions by different people without controlling for other variables that could have affected the amount of EPO produced per gene copy. *Id.* at 1095-98, 1091 (explaining that Dr. Kingston's comparison did not account for the different growing conditions, different promoters, and many other variables in the experiment that are evidenced by the thousand-fold variance in data points for one construct and pointing out that Kingston relied on only a single data point); Wall Test., R. Trial Tr. at 1155, 1157-1158 (objecting to Dr. Kingston's conclusions because there is not

a reliably established significant difference; "you can't really compare these two cells. They're like apples and oranges" due to "time differences" and a "large number of variables that could affect the expression level of EPO in those cells"); *cf.* Kingston Test., R. Trial Tr. at 190-91, 199-202, 205-06 (conceding that no other experiments were conducted, that the experiments were based on a single data point, and that he could not do a statistical analysis to determine if there was an outlier, but asserting that he still considered them to be controlled experiments); Kingston Test., Trial Tr. at 1484-85, 1490-91 (acknowledging that factors other than "neighborhood" effects can affect the amount of EPO produced per gene copy). Even Dr. Kingston admitted that a failure to use controls can lead to erroneous or misleading results and that a competent technician controls for the variables that could cause certain results. Kingston Test., R. Trial Tr. at 120: 10-18, 119: 9-120: 3. Furthermore, the evidence at trial suggested that HMR/TKT's experimental data itself was inconsistent. A single data point was an 800-fold difference from all the other data points—a variance greater than the alleged 500-fold difference between the single data point for pREPO26 and the highest value reported for pREPO22. Kingston Test., R. Trial Tr. at 190: 16-25, 201: 1-10; *see also* 12-17-96 Memo from Fike to Hermentin, Ex. 165. Thus, there is no reliable experimental data supporting the contention that it is the neighborhood, as opposed to some other factor, that accounts for HMR/TKT's expression capabilities.

Third, even if HMR/TKT had proven that the genomic EPO regulatory sequences in the EPO neighborhood—and not other factors like nutritional growth conditions, limits in cellular folding, strength of promoter, number of enhancers, and the Kozak sequence—affected the amount of EPO produced per gene copy, that would not have proved a meaningful change or substantial difference in actual EPO production. *SRI Int'l*, 775 F.2d at 1123; *cf. Winans*, 56 U.S. at 342-343. The evidence shows that HMR/TKT's R223 cells do not

produce more EPO or better EPO, even though they make more EPO per gene copy than the cells made following example 10 in Amgen's patent.[112] Lodish Test., Trial Tr. at 178: 4-12; Wall Test., R. Trial at 1155: 4-9, 1156: 23- 1157: 1 (noting that the difference is not significant). Indeed, Dr. Kingston admitted that actual EPO production levels by Amgen's example 10 cells and R223 cells were comparable. Kingston Test., R. Trial Tr. at 177: 25-178: 16. Moreover, uncontradicted testimony adduced at trial shows that there was no difference in biological activity or therapeutic effects of the EPO glycoprotein ultimately secreted by the two cells. Lodish Test., Trial Tr. at 166: 15-25. Given the claims, the specification, and the absence of any language about gene copy number, how efficiently the EPO is made is simply not material.[113] HMR/TKT points to nothing in the specification or prosecution history to suggest otherwise. As both Dr. Lodish and Dr. Wall testified, a more significant comparison would be between the amounts of EPO made by the respective cells or even between the rates of expression of EPO per million cells per 24 hours in the respective parties' processes—not the amount of EPO produced per gene copy. Wall Test., R. Trial Tr. at 1155: 4-9; Lodish Test., R. Trial Tr. at 1085: 13. Moreover, even if a comparison of the amount of EPO produced per gene copy was a material one, and if such a comparison had been conducted using controls, HMR/TKT's argument would likely still fail. HMR/TKT compares its cells to the cells in an example when it is clear, as Amgen argues, that "Dr. Lin's patent describes and teaches much

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[112] Dr. Lodish pointed out that both cell types contain the same expression construct; the R223 cells simply contain more copies of it. Lodish Test., Trial Tr. at 163: 16-18. This, however, does not amount to a functional difference in the cells' ability to produce EPO. *Id.* at 178: 4-12.

[113] Even if it was material, HMR/TKT has still not met its burden because, as discussed immediately above, much evidence was presented that factors other than the neighborhood could cause the differences in EPO production efficiency and Dr. Kingston did not control for these factors.

more—including various cultured vertebrate and mammalian cells, including human cells, grown in optimized nutrient conditions having stronger and/or more numerous viral promoters and enhancers." Amgen's Reply to HMR/TKT's Findings of Fact ¶ 101; *see also* Wall Test., R. Trial Tr. at 1161: 8-13.

Had HMR/TKT proven that its new technology of using homologous recombination or endogenous activation actually worked in some substantially different way due to the neighborhood and enabled it to produce significantly more EPO or EPO that somehow differed in its biologic or therapeutic effects (which would have supported HMR/TKT's contention that its technology functions differently), it might well have demonstrated sufficient grounds for invoking the reverse doctrine of equivalents. *Cf. Scripps*, 927 F.2d at 1565 (noting that whether alleged infringer's new recombinant technology resulted in "specific activities and purity" otherwise unattainable might, if proven, provide sufficient grounds for invoking the reverse doctrine of equivalents). Here, however, HMR/TKT has not done so. It has not shown that any of these differences constitute a radical or dramatic improvement or are "so far changed in principal that they perform the function in a substantially different way." *SRI Int'l*, 775 F.2d at 1124.

Thus, despite the fact that HMR/TKT's process employs homologous recombination and endogenous DNA and produces more EPO per gene copy than Amgen's Example 10 cells, it appears that its process does exactly that which Amgen's patent teaches: it introduces a strong viral promoter and non-human enhancers to overcome the naturally restrictive neighborhood in the R223 cells. *See* Wall Test., R. Trial Tr. at 1149: 3-14, 1159: 6-1161: 13; Lodish Test., R. Trial Tr.

at 1097; Lodish Test., Trial Tr. at 165: 1-11, 178: 4-12; Kingston Test., Trial Tr. at 1382-1386.[114]

(2) Different Promoter Placement, Splice Sites, and Leader Sequences

HMR/TKT argues that it places its promoter much farther upstream of the EPO gene to be expressed than does Amgen and that this was something those skilled in the art in 1984 would not have dared to attempt. HMR/TKT's Opening Br. After Trial at 13. As a result, it contends, HMR/TKT's process for producing EPO uses primary RNA transcripts and splice sites that differ from those used in Amgen's process, and results in a different EPO mRNA in HMR/TKT's and Amgen's cells and a different primary EPO protein product. HMR/TKT's Proposed Findings of Fact at 33-36; HMR/TKT's Opening Br. After Trial at 15.

(a) Upstream Promoter Placement and Splice Sites

Although it is undisputed that HMR/TKT places its promoter much farther upstream than 44 base pairs (the position described in one example in Amgen's specification), the Court has now found that placement of the promoter further upstream of the EPO coding region and splicing out deleterious ATGs was indeed a concept known and understood to those skilled in the art at the time Amgen filed its application (1983-84).[115] Furthermore, the Court has held that Amgen's

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[114] To be clear, none of the examples requires that the EPO coding sequences be "cut away" from their native regulatory sequences. To the contrary, according to Dr. Wall, Example 10 retains a downstream native EPO regulatory sequence—the hyposix inducible element ("HIE"). Wall Test., R. Trial Tr. at 1128: 10-1129: 1.

[115] As noted earlier, HMR/TKT offers no support—except previous statements by this Court—for its assertion that no one skilled in the art could have or would have in 1984 dared to place the promoter so far upstream from the coding sequence.

process covers, adequately describes, and enables such upstream promoter placement.

In terms of the EPO splice donor sites, it is undisputed that absent the exons, the splice donor sites are the same and that the intended effect of both processes was to splice out what is in between including intervening sequences and any deleterious ATGs. *See, e.g.*, Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1-22, 1440: 19-25, 2094-2102 (admitting that what HMR/TKT labeled as its splice donor site is identical to the human splice donor site disclosed by Amgen in Figure 6). HMR/TKT argues, however, that its splice site is not the same as Amgen's because the left portion (the exon) is different. HMR/TKT's Opening Br. After Trial at 15; HMR/TKT's Proposed Findings of Fact at 35. It asserts that "it is the exon portion that matters" because it creates the leader sequence for the expressed polypeptide, that is, the exons remain to encode the polypeptide while the introns are removed. HMR/TKT's Opening Br. After Trial at 15. Amgen argues that the exon is irrelevant and not part of the splice site. Therefore, the key factual question for the Court is whether exons are included when one skilled in the art refers to the splice sites.

To the extent that the experts disagreed, the Court credits Dr. Lodish's testimony explaining that the exons are not included. Lodish Test., R. Trial Tr. at 1107-10; *id.* at 1132-33 (explaining that it is the splice donor sequence, not the splice junction, that will determine where downstream and with what corresponding DNA downstream a splice junction will splice and stating that "the splice donor is the sequence . . . that is removed during the splicing process," the splice acceptor is the sequence that is removed downstream, and "it's the regions on either side that are linked together"). This accreditation of Dr. Lodish's testimony is supported by evidence that HMR/TKT itself did not consider the hgH exon 1 to be part of the splice donor sequence. In its Investigational

New Drug Application (IND) and in its patent, HMR/TKT identifies the splice donor site to be separate from the growth hormone exon 1 sequence. *See, e.g.*, HMR/TKT's IND, Ex. 19, at 554; HRM/TKT's IND, Ex. 20, at 830; U.S. Patent No. 5,641,670 ("Treco's Patent"), Ex. 12, col. 50: 53-55; *see also* Kingston Test., Trial Tr. at 2094-2102 (conceding that this interpretation of the IND and patent is correct—that is, that HMR/TKT did not include the three nucleotides in exon 1 as part of the splice donor sequence). Moreover, in the IND, HMR/TKT identifies the splice donor sequence to be the first 10 nucleotides of intron 1: GTGAGTACTC, which is identical to the sequence in Amgen's patent. *See, e.g.*, HMR/TKT's IND, Ex. 19, at 554; HRM/TKT's IND, Ex. 20, at 830; *see also* Demonstrative Aids 7 & 8 from Lodish Rebuttal Examination, R. Trial.

Thus, as alluded to earlier in the written description analysis, this Court finds that the fair preponderance of the evidence shows, by a slight margin, that HMR 4396 uses the same splice donor site as that disclosed in Amgen's specification. Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1- 22, 1440: 19-25 (admitting that absent the exons, the splice donor sites were the same and that the intended effect was to splice out what is in between, including intervening sequences and the deleterious ATGs). The only difference is that Amgen takes the genomic EPO splice donor site disclosed in Amgen's Figure 6 and moves it upstream. Placing the promoter further upstream of DNA encoding a protein using the identical splice site is simply not a fundamental change in principal, because the intervening DNA is spliced out when the mRNA is formed. As discussed *supra*, skilled artisans could have done this at the time Amgen filed its application, and, more importantly, skilled artisans could easily have done it at the time of the alleged infringement—the relevant time period for analyzing equivalent infringement. *Warner-Jenkinson*, 520 U.S. at 37. Therefore, it is unclear how HMR/TKT can argue that its promoter place-

ment differentiates its process from Amgen's process. As the Federal Circuit pointed out when HMR/TKT made the same argument in furtherance of the reverse doctrine of equivalents with respect to the '349 product claims, the exact promoter placement or the way the accused device controls transcription is not relevant to the analysis because neither the claims nor the specification require a locational limitation. They merely call for "operative linkage," which was construed by the Court to mean "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen*, 126 F. Supp. 2d at 90. It refused to read any distance restriction in the claim term "operatively linked," because the specification does not restrict the promoter location. It merely communicates that in order to achieve "operative link[age]," what is important is placing a strong promoter upstream of the ATG initiating codon of the EPO gene and splicing out unwanted ATGs. Thus, that which HMR/TKT does was "suggested" by the patent. *Westinghouse*, 170 U.S. at 573 ("If the method pursued by the patentee for the performance of the function discovered by him would naturally have suggested the device adopted by the defendants, that is in itself evidence of intended infringement."). Thus, HMR/TKT has not shown any real difference, let alone a substantial or radical one.[116]

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[116] HMR/TKT argues that its upstream promoter placement and the difference in the type of promoter optimize its process, and it cites testimony by Dr. Lodish and Dr. Wall admitting that the location and strength of the promoter affect the promoter's activity. *See, e.g.*, HMR/TKT's Findings of Fact ¶¶ 117, 119. These arguments, however, fail to justify evocation of the doctrine for the same reasons discussed earlier. First, mere improvement or superiority is not enough. Second, it is unclear that HMR/TKT has shown any relevant optimization, since increased EPO production or quality is not claimed. Third, the location of the promoter or type of strong viral promoter are not specifically claimed or defined by the specification.

(b) Different Leader Sequences in the Primary EPO Protein Product

HMR/TKT argues that its primary EPO protein product is different from Amgen's product because it contains a hybrid leader sequence containing both hGH and human EPO amino acids, whereas Amgen's only contains EPO leader sequences. HMR/TKT's Proposed Findings of Fact at 36; HMR/TKT's Opening Br. After Trial at 15.[117] At trial, Dr. Lodish conceded that in Amgen's Example 10, exon 1 comes from the EPO gene whereas in HMR/TKT's process, it comes from the human growth hormone gene. Lodish Test., Trial Tr. at 174. He explained that the difference between the leader peptides is a "minor" one because they both function in exactly the same way and both are removed. *Id.*; *see also id.* at 433-34 (stating that the leader peptides are different but perform the same function and are ultimately cleaved); *id.* at 159-160. Evidently, exons 2-5 of the EPO structural genes are what encode amino acids in the mature secreted form of the protein. *Id.* at 173; *id.* at 160 ("[E]xon 1 . . . encodes part of the leader peptide which is removed from the cell and has no other function."). Furthermore, what is ultimately secreted from the cell is the same polypeptide with three n-linked oligosacharides, sialic acids . . . and one o-linked oligosaccharide." *Id.* at 174; *id.* at 160 ("Exon 1 . . . has no effect whatsoever on the secreted mature EPO glycoprotein."). HMR/TKT points to no evidence disputing this testimony nor does it even attempt to explain how this difference presents a change in principle from Amgen's patented process.

(3) Method of Growing Cells

HMR/TKT argues that it grows its cells in a substantially different manner from that described in the '698 patent.

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[117] This involves the step of translation. When the messenger RNA is translated, the result is a polypeptide which has a leader sequence. Kingston Test., R. Trial Tr. at 53: 2-4. During HMR/TKT's translation, the leader sequence contains both the hGH and human EPO amino acids. *Id.*

HMR/TKT's Opening Br. After Trial at 18-19; HMR/TKT's Proposed Findings of Fact at 38-41. It points out that Amgen's specification describes a process of growing vertebrate cells that uses a roller bottle system to obtain adhesion of the cell line to the bottle surface. HMR/TKT's Opening Br. After Trial at 19. HMR/TKT, on the other hand, uses an air-lift technology that "works in a completely different way from roller bottle technology". *Id.*

These arguments fail for the same reasons that all of HMR/TKT's other reverse doctrine of equivalents arguments fail. First, HMR/TKT compares its process to the method of culturing described in an embodiment in the specification instead of to the spirit and intent of the claims. Second, it has not even argued how its culturing process is changed in principle from that explicated in Amgen's patent.

The Court begins by pointing out that it has not construed the claims to require roller bottle culturing. Nor has HMR/TKT pointed to anything in the patent, specification, or prosecution history to compel it to do so. HMR/TKT simply argues that because a roller bottle system is the only type of culturing actually described in the specification, the claims should be limited to this type of culturing. The Court has already explained at length that a patent's scope is not limited to those embodiments described in the specification, absent concerns about invalidity, prosecution history estoppel, or other such grounds.

Moreover, after a careful review of the specification, it is clear that it does anything but imply that use of roller bottles is the only way to culture or grow the cells. The specification states that productivity can be improved "by appropriate cell culture techniques." '933 Patent, Ex. 1, col. 27: 7-9. Then it makes a general statement that "[the] propagation of mammalian cells in culture generally requires the presence of serum in the growth media," but that "a method" that does not contain serum can "greatly facilitate" the process. *Id.* at col.

27: 10-14 (emphasis added). The implication of these two sentences is (a) more than one culturing technique is contemplated, and (b) both serum and serum-free culturing can be used to propagate mammalian cells, but serum-free is preferred. The specification then goes on to describe one such preferred method that happens to use roller bottles. *Id.* at col. 27: 15-53. Later, the specification also teaches, in the preferred method, growing suspension cell cultures in spinner flasks--yet another type of culturing or growing process. *Id.* at col. 27: 19-21. Thus, the specification does not only teach culturing via the roller-bottle but also teaches culturing in spinner flasks.[118] Indeed, HMR/TKT's expert testimony confirms this interpretation of the specification. *See* Hancock Test., R. Trial Tr. at 259: 20-260: 21, 262: 16-263: 24 (admitting that in 1984 roller-bottles were not the only method for culturing mammalian cells and that the specification teaches growing up the suspension cell cultures in spinner flasks, which grow the cells in suspension).

Since HMR/TKT points to nothing in the patent or prosecution history to support adding a limitation to the claims, the Court refuses to do so. The equitable scope of the claim is broader than roller-bottle culturing. *Scripps*, 927 F.2d at 1581 (weighing accused device against equitable scope of the claims); Sirilla, Feddo & Antone, *supra*, at 101.

Even if the Court were to limit the claims to a roller bottle system of culturing, HRM/TKT would still fall short of making a prima facie showing that the reverse doctrine of equivalents is applicable. HMR/TKT does not even attempt to explain how using an air-lift fermenter to grow its cells (as opposed to roller bottles) justifies invoking the reverse doc-

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[118] That this other type of culturing is described during the preparatory stage does not change the analysis because, according to HMR/TKT's expert, the cells are "growing" and producing EPO in the preparatory stage. Hancock Test., R. Trial Tr. at 263: 3-264: 11. Therefore, this culturing method can be deemed part of the "growing" step described in the claims.

trine of equivalents, that is, it does not show how this difference is a "manifest departure in principle" or even novel, for that matter. *Westinghouse*, 170 U.S. 572, 579. Instead, it spent many of its precious trial minutes[119] eliciting testimony about the minute distinctions between air-lift fermenting and roller-bottle culturing. *See generally* Hancock Test., R. Trial Tr. at 232-39. For example, it showed at trial that (a) the cells circulate through the fermenter, but adhere as a layer to the surface of the roller bottles; (b) roller bottle culturing uses fetal calf serum, while the air-lift technology does not; (c) roller bottle culturing is done horizontally, while air-lift fermenting is done vertically; and (d) multiple bottles are used in roller bottle culturing, while only a single vessel is used in air-lift fermentation. *Id.* at 234, 236-40. HMR/TKT failed, however, to demonstrate that the two processes are premised on anything other than the same principle of mixing cell cultures.

Indeed, HMR/TKT did not even show that air-lift fermenting was superior let alone a substantial or radical improvement. Dr. Hancock basically testified as to how the processes were different, but said nothing about how these differences mattered. *See generally* Hancock Test., R. Trial Tr. at 232-39. True, Dr. Hancock testified there is a risk of contamination when using fetal calf serum and that the air-lift fermenter allows for more uniform monitoring and control of conditions since it only uses one vessel. *Id.* at 234-35, 241, 256; *see also id.* at 238-399. He did not, however, loop it back together. He

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[119] This trial, as indeed all civil trials in this session of the Court, was conducted pursuant to strict overall time limits established by the parties pre-trial and confirmed by order of the Court. Reasonable time limits have been confirmed by the nation's most thoughtful commentators as a trial technique that enhances the quality of justice and improves the administrative aspects of any civil trial. The Vanishing Trial, Discussion at the ABA Section on Litigation Symposium (Dec. 12-14, 2003). The Court has long followed this salutary practice. *Lareau* v. *Page*, 840 F. Supp. 920, 933-35 (D. Mass. 1993).

did not present or refer to any controlled experimental data comparing the two processes that showed that fetal calf serum caused contamination that affected the process. *Id.* at 256-57. Moreover, he did not testify as to how or even whether the additional level of control in air-lift fermenting is beneficial or superior. *Id.* at 239. He merely made some vague statements that in the air lift fermentation technology, the process could potentially be optimized because the medium can be defined. *Id.* at 242-43. Even if there had been a more concrete showing that serum-free medium was advantageous to fetal-calf serum medium, it would not have been enough to show a substantial change or manifest departure in principle. As discussed earlier, the mere fact that something is improved or better does not justify invoking the reverse doctrine. *See, e.g., Studiengesellschaft*, 726 F.2d at 728; *Phillips Petroleum Co.*, 673 F. Supp. 1278.

Further, HMR/TKT's own expert implicitly admitted that growing cells in an air-lift fermenter is *equivalent* to many culture methods including the roller bottles or spinner flasks exemplified in Amgen's patent. Hancock Test., R. Trial Tr. at 264: 12-265: 12, 261: 23-262: 24 (conceding that regardless of whether roller bottle spinner cells are used or other types of culturing techniques, the objectives are the same and can be met by mixing or agitating the cell culture by spinning, rolling, or mixing it with air bubbles from an air-lift fermenter).

As the Federal Circuit has noted many times in the past, "[e]quivalence and non-equivalence, as the terms indicate, are but opposite sides of the same coin." *SRI International*, 775 F.2d at 1125; *id.* at 1125 n.22 ("In both instances, one is dealing with whether a particular product falls within a *range* of products which the patent entitles the patentee to exclude others from making, using, or selling."); *see Westinghouse*, 170 U.S. at 568; *Texas Instruments II*, 846 F.2d at 1371; Duffy, *supra*, at 315. Since air-lift fermenting is essentially

equivalent to roller-bottle culturing and is premised on the same principle of mixing cell cultures, it cannot qualify as a "reverse equivalent." *SDS USA, Inc.*, 122 F. Supp. 2d at 541; *see also Westinghouse*, 170 U.S. at 569 (explaining that if the substance of the invention is there, "[m]ere variations of form may be disregarded").[120]

(4) HMR/TKT's Process Was Patented

HMR/TKT seems to believe that since the United States Patent and Trademark Office granted it a patent on its culturing process, the two processes must be so substantially different that the reverse doctrine of equivalents can justifiably be invoked. *See, e.g.*, HMR/TKT's Reply Br. After Trial at 28; HMR/TKT's Proposed Findings of Fact ¶ 121. While attainment of a patent may aid in making a prima facie case in support of the reverse doctrine of equivalents, *see, e.g.*, *Jewish Hosp. of St. Louis* v. *IDEXX Laboratories*, 973 F. Supp. 24, 28 (D. Me. 1997) (finding a prima facie showing met when one of three facts asserted was that the process was patented), it does not necessarily equate to such a determination. *See, e.g.*, *Nat'l Presto Indus., Inc.* v. *West Bend Co.*, 76 F.3d 1185, 1191-92 (Fed. Cir. 1996) ("The grant of a separate patent on the accused device does not automatically avoid infringement, either literal or by equivalency. Improvements or modifications may indeed be separately patentable if the requirements of patentability are met, yet the device may or may not avoid infringement of the prior patent."); *Atlas Powder Co.* v. *E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 1580-81 (Fed. Cir. 1984) (finding equivalent infringement despite the fact that the accused device was

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[120] The Court's conclusion that HMR/TKT's mode of culturing is not "so far changed in principle" or "substantially different" finds further support in the fact that HMR/TKT's expert stated that HMR/TKT itself employs roller bottle culturing in an early stage of its manufacturing process. Hancock Test., R. Trial Tr. at 265: 13-266: 13; HMR/TKT's IND, Ex. 19, at 566, 574.

separately patented). Thus, as Amgen contends, "patents are routinely granted for improvements in technology even though the practice of the technology would infringe an earlier issued patent." Amgen's Reply to HMR/TKT's Opening Br. After Trial at 29; *see also* Lemley, *Economics*, *supra*, at 1009 (not-ing that "patenting an improvement does not prevent it from infringing on the original patent" and describing three situations where "an improvement which is nonobvious in view of the prior art can still infringe on a patent which is part of that prior art"); *see also* Merges & Nelson, *supra*, at 865 ("Issuance of an improvement patent or a holding that a patent is valid but subservient to another patent is . . . common."). Indeed, here it appears that HMR/TKT's patent consists of claims that are narrower but within the scope of Amgen's broader patent since its claims relate to homologous recombinant cells comprising a targeting sequence, an "exogenous regulatory sequence, an exogenous exon, and a splice-donor site operatively linked to the second exon of an exogenous gene." Treco's Patent, Ex. 12, col. 63: 50-54. Thus, without more, the fact that its process has been patented fails to make HMR/TKT's case.

c. Conclusion

HMR/TKT has succeeded in proving that its process differs in many respects from those specifically exemplified in the Amgen's specification and even is advanced technologically in at least one way. As the Supreme Court explained in *Graver Tank*, however,

> Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose in every respect. In determining equivalents, things equal to the same thing may not be equal to each other and, by the same token, things for most purposes different may sometimes be equivalents. Consideration must be given to the purpose for which [some aspect of

> the invention] is used in a patent, the qualities it has when combined with the other [aspects], and the function which it is intended to perform.

339 U.S. at 609; *see SRI International*, 775 F.2d at 1124. Here, taken together, the accumulated differences between the accused device and Amgen's invention—as described in the patent, the claims, and the specification—are not *substantial*; that is, they do not show that any principal has been *so far* changed such that it would be inequitable to view HMR/TKT's invention as within the scope of the claims of the '698 patent. *Studiengesellschaft*, 726 F.2d at 728 (considering whether there is so much dissimilarity that it would be inequitable to regard the infringing invention as within the scope of the claims); *see also Westinghouse*, 170 U.S. at 568 (considering whether the claims cease to represent the invention).

While the Court affirms the viability of the reverse doctrine of equivalents for those rare cases where the claims read on a new device or process despite its use of a new technology that makes a real difference in how the process works or what is produced, HMR/TKT has failed to meet its burden in establishing the defense here (although the neighborhood theory potentially could have carried the day, had it been thoroughly demonstrated through experimentation at trial).

5. Ultimate Conclusion Concerning Infringement of the '698 Process Patent

The Court holds that Amgen has carried its burden of proving by a fair preponderance of the evidence that HMR/TKT's process infringes the '698 patent, claims 4-9.

B. The '349 Patent: Claim 7

1. Background

In *Amgen I*, the Court held that HMR/TKT did not literally or equivalently infringe claim 7, the process claim, of the

'349 patent. *Amgen I*, 126 F. Supp. 2d at 122.[121] In reaching this determination, the Court compared the accused process to the preferred embodiment in the specification and concluded that "[HMR/]TKT's process for producing erythropoietin differs markedly from that disclosed by Amgen's specification" because it "utilizes the endogenous rather than exogenous EPO gene" and it "places its promoter upstream from, rather than adjacent to, the EPO gene." *Id.* The Federal Circuit, as it did with the Court's holding of infringement of the '698 patent, vacated this holding and remanded it so that the Court could analyze infringement by comparing the accused process to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1313, 1347, 1351.

Since the Court heard the entirety of both parties' arguments and evidence concerning the '349 patent at the first trial, no new evidence with respect to this patent was taken on remand. The parties, however, were given the opportunity to brief the issues remanded to this Court in pre and post-trial memoranda. Before the Court are both parties' motions for judgment pursuant to rule 52(c) [Doc. Nos. 674 & 686].

In HMR/TKT's motion for judgment pursuant to rule 52(c), it argued a new defense, the reverse doctrine of equivalents. Although the Court allowed the defense as it related to the '698 patent, it did not definitively do so for the '349 patent, because the procedural postures of the two patents were different. HMR/TKT never had a chance to present its case of non-infringement with regard to the '698 patent in *Amgen I*, but it did with regard to the '349 patent. As it ends up, this procedural dispute is moot. Even if the Court were to allow the defense at this stage, it would fail for lack of merit.

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[121] As discussed earlier, the Court held and the Federal Circuit affirmed that HMR/TKT literally infringed claims 1, 3, 4, and 6. *Amgen I*, 126 F. Supp. 2d at 117-18; *Amgen II*, 314 F.3d at 1351-52. Thus, the only issues remaining regarding this patent concern claim 7, the process claim.

2. The Claim At Issue

Amgen's '349 patent contains six product claims regarding types of vertebrate cells grown in culture and one process claim, claim 7. The issue is whether HMR/TKT infringed claim 7, the process claim:

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.

'349 Patent, Ex. 1, col. 38: 34-36.

3. Literal Infringement

a. Discussion

Since literal infringement of claims 1, 2, 4, and 6 has been established and affirmed, *Amgen II*, 314 F.3d at 1352, 1358, to prevail on this issue, Amgen need only show by a fair preponderance of the evidence that HMR/TKT's process for producing EPO comprises "culturing under suitable nutrient conditions, vertebrate cells." Here, it is clear that Amgen has met its burden.

First, Dr. Lodish specifically testified that "I guess there is no dispute that [HMR/TKT's] cells are cultured and they're clearly vertebrate cells." Amgen's '349 App., Tab I (Lodish Test., Trial Tr.) at 300: 22-301: 8. HMR/TKT's assertion that Dr. Lodish's testimony makes clear that he was only guessing does not cast any affirmative doubt on Dr. Lodish's statements, which this Court credits.

Second, as discussed earlier, the Joint Pretrial Memorandum itself states that HMR/TKT's HMR 4396 is produced by "growing, under suitable nutrient conditions R223 cells," Amgen's '349 App., Tab M (4/26/00 Corrected Joint Pretrial Mem.), ¶ 25, and that its cells are cultured, *id.* ¶ 13 ("HMR 4396 is produced from the R223 cell line grown in culture."). Since HMR/TKT has admitted in various contexts that culturing and growing basically mean the same thing, it has

implicitly admitted that its process literally infringes claim 7.[122]

Last, this Court's factual findings support the holding that HMR/TKT's process cultures the cells. In finding literal infringement of claims 1 and 4 of the '349 patent, this Court found that HMR/TKT's R223 cells are "capable, upon growth in culture, of producing erythropoietin in the medium of their growth in excess of 100 units of erythropoietin per 10 cells in forty-eight hours as determined by RIA (radioimmunoassay)," just like Amgen's cells. *Amgen I*, 126 F. Supp. 2d at 119. Thus, the Court finds that HMR/TKT's cells are cultured.

Tellingly, HMR/TKT did not even argue in its post-trial submissions that its process did not literally infringe claim 7 of the '349 patent.

b. Conclusion Concerning Infringement: '349 Patent, Claim 7

Amgen has shown by a fair preponderance of the evidence that HMR/TKT's HMR 4396 literally infringes claim 7 of the '349 patent.

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[122] In one of its claim construction submissions, HMR/TKT proffered that "culturing under suitable nutrient conditions" means the same things as "growing in vitro, under suitable nutrient conditions. 10/18/99 Amgen's Claim Construction Submission, Ex. A, at 5. In its memorandum in support of its step-plus-function arguments regarding the '349 and '698 patent, HMR/TKT asserted the exact same arguments with regard to the step of growing and the step of culturing.

Experts also used the two words interchangeably. Dr. Tlsty stated that he had been "growing and culturing cells since [he] was an undergraduate." Amgen's Opp'n at 13; Tlsty Test., Trial Tr. at 832: 1-16; *see also* HMR/TKT's IND, Ex. 19, at 574 (describing the culturing of HMR/TKT's R223 cells).

4. Reverse Doctrine of Equivalents

HMR/TKT presented the exact same arguments in furtherance of its reverse doctrine of equivalents arguments for the '349 patent as it did for the '698 patent. Given that it points to nothing in the claims or prosecution history of the '349 patent specifically in support, and the specifications are the same as between the two patents, the above analysis with respect to the '698 patent applies here.[123]

5. Ultimate Conclusion Concerning Infringement of Claim 7 of the '349 Patent

The Court rules that Amgen has shown by a fair preponderance of the evidence that HMR/TKT's process literally infringes Amgen's '349 patent. Therefore, HMR/TKT's Fed. R. Civ. P. 52(c) motion regarding infringement of the'349 patent [Doc. No. 686] is DENIED and Amgen's Fed. R. Civ. P. 52(c) motion regarding infringement of the '349 patent [Doc. No. 674] is ALLOWED.

VI. VALIDITY CHALLENGES UNDER 35 U.S.C. §§ 102(a) & 103

HMR/TKT argues that the asserted claims of the '422, '080, '698, and '349 patents are either anticipated or rendered obvious by Sugimoto, Goldwasser, or both. Since these patents are presumed valid, HMR/TKT bears the burden of proving its contentions by clear and convincing evidence. 35 U.S.C. § 282 (2000); *Amgen II*, 314 F.3d at 1335.

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[123] Indeed, it is even less appropriate to apply the reverse doctrine of equivalents with respect to the '349 patent than with respect to the '698 patent, since these same reverse doctrine arguments were made and rejected by the Federal Circuit with respect to the product claims of the '349 patent, and, as mentioned earlier, HMR/TKT has not adduced, nor has the Court found, any case law suggesting that process patents should be analyzed differently than product patents.

A. Sugimoto

1. Background

a. Overview of Sugimoto

U.S. Patent No. 4,377,513 (Sugimoto's patent) was filed in 1981 and issued to Sugimoto on March 22, 1983. Sugimoto's patent, Ex. 2229, at 1. Sugimoto claims a process for producing human erythropoietin comprising "multiplying human lymphoblastoid cells capable of producing erythropoietin by transplanting said cells into a non-human warm-blooded animal body," or, alternatively, multiplying said cells "by allowing said cells to multiply with a device by which the nutrient body fluid of a nonhuman warm-blooded animal is supplied to said cells," and allowing the cells multiplied by either of the above multiplications procedures to release human erythropoietin. *Id.* at col. 6: 46-59. Put another way, Sugimoto claims that when a human cell line that produces EPO is fused with a human lymphoblastoid cell line, the resulting fused cells produce higher amounts of EPO in culture than the original fusion partners. *Amgen I*, 126 F. Supp. 2d at 108. Sugimoto also advises that (1) conventional techniques can be utilized to achieve purification; and (2) human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Sugimoto's patent, Ex. 2229, col. 3: 50-55; col. 3: 66-4: 2.

b. The Court's Decisions in *Amgen I*

(1) Anticipation

This Court held that HMR/TKT failed to show by clear and convincing evidence that Sugimoto's patent anticipated Amgen's '422, '080, and '349 patents. *Id.* at 110. In support of this holding, it found that Sugimoto was not enabled and that none of the cited references disclose each and every limitation of any of Amgen's individual claims. *Id.* at 109. With respect specifically to claim 1 of the '422 patent, the

Court found that none of the cited references disclose a therapeutically effective amount of EPO or the purification of human EPO from mammalian cells grown in culture. *Id.*

(2) Obviousness

Because the Court had already held that HMR/TKT failed to prove that Sugimoto was enabled, it held that Amgen's claims were also not invalid due to obviousness. The Court noted in a footnote, however, that had the Court found the Sugimoto patent enabled, it would have "go[ne] a long way toward proving HMR/TKT's obviousness defense." *Id.* at 114. This is because the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. The Court noted that if one of ordinary skill could actually make the EPO-producing cells described in the Sugimoto patent, a point on which HMR/TKT failed to persuade this Court, such a combination of prior art material might render invalid the pharmaceutical composition claims of the '080, and '422 patents. *Amgen I*, 126 F. Supp. 2d at 114 n.29. Finally, the Court noted that secondary considerations also applied to support the Court's findings of non-obviousness.

c. The Federal Circuit's Opinion

The Federal Circuit ruled that the Court erred in placing the burden of proving enablement of Sugimoto on HMR/TKT. *Amgen II*, 314 F.3d at 1354. The Federal Circuit explained that in prosecution of a patent, the examiner can reject applications as anticipated by prior art without first having determined whether that application had been enabled. The patent applicant can then overcome such a rejection by proving that the prior art had itself not been enabled. The Federal Circuit reasoned that this type of burden shifting was appropriate in this context as well. Therefore, it held "that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and

claimed) material in the prior art patent defendant asserts against a plaintiff." *Id.* at 1355.[124] The patentee, however, may prove nonenablement by a fair preponderance of the evidence. *See id.* Thus, the Federal Circuit concluded, Amgen is the party that bears the burden of proving the non-enablement of Sugimoto. *Id.*

The Federal Circuit noted that the Court could not have found that Amgen met its burden based solely on Dr. Erslev's testimony that "no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by Sugimoto procedure." *Id.* at 1356. "The mere fact that no one has so used the Sugimoto process is only minimally probative of non-enablement: a conclusion that no one *could have* used Sugimoto." *Id.* at 1356. Moreover, the Federal Circuit stated, the fact that Amgen argued non-enablement of Sugimoto before the patent examiner during prosecution of Amgen's patents is only minimally probative of the issue since this was only one argument out of many and "we cannot assume the acceptance of every argument presented during prosecution." *Id.* Thus, the Federal Circuit concluded that Amgen had not presented evidence sufficient to meet its burden.

The Federal Circuit clarified that the Court's error was harmless for the most part because the Court had conducted a detailed anticipation analysis. With respect to claim 1 of the '422 patent, however, the Federal Circuit directed the Court to consider, on remand, whether it is novel over Sugimoto in light of the Court's new definition of "therapeutically effective" while being "mindful of the principle that source limitations cannot impart novelty to old compositions." *Id.*

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[124] As is so frequently the case in the patent area, this is not a true presumption at all, *see* Fed. R. Evid. 301, but rather a burden shifting mechanism that places the burden of proving nonenablement on the patentee. For criticism of this recurrent imprecision in language, *see Amgen III*, 287 F. Supp. 2d at 131.

Additionally, the Federal Circuit remanded to this Court the issue of obviousness in light of Sugimoto, because a reference need not be enabled to prove invalidity under section 103. *Id.* at 1537.

2. The Claims at Issue

HMR/TKT argues that Sugimoto (1) anticipates claim 1 of the '422 patent and claims 6 and 9 of the '698 patent and (2) renders obvious claim 1 of the '422 patent, claims 2-4 of the '080 patent, and the asserted claims of the '349 and '698 patents.

3. Discussion

a. Anticipation: Does Sugimoto Anticipate Any of the Asserted Claims of the '422 and '698 Patents?

"[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc.* v. *Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citing *Atlas Powder Co.* v. *Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999)); *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The invention at issue must be identical to that in a single prior art reference and it must be shown in as complete detail. *Richardson* v. *Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Determining whether a patent is invalid by anticipation in prior art is matter of fact, *Advanced Display*, 212 F.3d at 1283, and the burden is placed on the party trying to prove anticipation. *Robotic Vision Sys., Inc.* v. *View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999). Hence, here HMR/TKT must prove anticipation by clear and convincing evidence.

(1) Has Amgen Shown that Sugimoto Was Not Enabled?

As the Federal Circuit explained in *Amgen II*, "a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to enable one of skill in the art to reduce the disclosed invention to practice." 314 F.3d at 1354 (internal quotations and citations omitted). Therefore, if Amgen shows by a preponderance of the evidence, that it "present[ed] evidence of nonenablement that [this Court] finds persuasive, the [Court] must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption [of enablement] has been overcome." *Id.* at 1355.[125]

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[125] HMR/TKT argues that Amgen's burden of proof is higher than proof by a fair preponderance of the evidence. *See* HMR/TKT's Reply Br. After Trial at 4 n.* (claiming it is one of "persuasive evidence"). The Court disagrees. First, it is unclear to what standard HMR/TKT believes Amgen should be held, since proof by a fair preponderance is by its very nature "persuasive." Second, the Federal Circuit indicated in *Amgen II* that the burden should be commensurate with that required of an applicant, before the PTO, to overcome a rejection for anticipation by proving non-enablement of the prior art. The Federal Circuit held that:

> an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. . . . Like the applicant in *ex parte* prosecution, . . . the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art.

Amgen II, 314 F.3d at 1355. Before making this holding, the Federal Circuit quoted the following from *In re Sasse*, 629 F.2d 675, 681 (C.C.P.A. 1980): "[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a *preponderance of the evidence.*" *Amgen II*, 314 F.3d at 1355 (quoting *In re Sasse*, 629 F.2d at 681) (internal quotation marks omitted) (emphasis added).

As applied to this case, the conclusion that Sugimoto is enabled may be rebutted by Amgen if it shows by a fair preponderance of the evidence

For the following reasons, the Court finds that Amgen has shown by a preponderance of the evidence that Sugimoto is not enabled—that is, that Sugimoto's specification does not teach skilled artisans how to make and use the entire scope of the claimed invention without undue experimentation. *See* 35 U.S.C. § 112, ¶ 1 (2000); *Genentech*, 108 F.3d at 1365 (quoting *In re Wright*, 999 F.2d at 1461); *Plant Genetic Systems*, 315 F.3d at 1339 (same).

(a) The Starting Materials Were Neither Described Nor Made Available to the Public

First, the Sugimoto starting materials were not deposited, not described so that one skilled in the art could obtain them, and not otherwise made available to the public. Both Dr. Lodish and Dr. Green testified that Sugimoto's failure to deposit the starting materials, or to make them available to the public in some way, was critical in this case, because Sugimoto also failed to describe the starting kidney cells in a manner that would enable one skilled in the art to reproduce the method. *See* Lodish Test., R. Trial Tr. at 287: 3-288: 16 (explaining that Sugimoto only loosely describes the kidney tumor cells as "carcinomas," when he should have characterized the cells as to karyotype and morphology so that one could repeat the experiments); Green Test., R. Trial Tr. at 421: 4-422: 2 (hypothesizing that one reason why HMR/TKT's attempts to reproduce Sugimoto's hybridization failed

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that it is not. *But see Halliburton* v. *Weatherford*, No. 302CV1347-N, 2003 WL 22017187, at *1-*2 (N. D. Tex. Aug. 26, 2003) (interpreting *Amgen II* to teach that the patentee only has the burden of going forward to pre-sent some material evidence which places the enablement of the prior art in question, i.e., the burden of production); *Abbott Labs.* v. *Diamedix Corp.*, 969 F. Supp. 1064 (N.D. Ill. 1997) (same); Chisum, *supra*, § 3.04(1)(b)(v) at 3-102, 3-103. While these sources are faithful to the import of the word "presumption" in the Federal Rules of Evidence, this Court reads *Amgen II* to shift the burden of persuasion as well.

might be that HMR/TKT was unable to obtain the starting kidney tumor line described by Sugimoto).

That this failure to teach how to obtain the starting materials or to deposit them was debilitating is evidenced by both parties' unsuccessful attempts to procure such cells. Amgen, after many attempts, was unsuccessful at locating or obtaining any of the human kidney tumor cells used by Sugimoto or any cells capable of producing EPO at the levels reported by Sugimoto in his patent. Lin Test., R. Trial Tr. at 562: 19-563: 11.[126] Moreover, as this Court found in *Amgen I*, after an arduous search, even HMR/TKT's star witness, Dr. Heartlein, was unable to obtain any of the human kidney tumor cells used by Sugimoto, 126 F. Supp. 2d at 109; Heartlein Test., Trial Tr. at 1812: 10-1813: 13; 1826: 5-1827: 24, and was unable to find any prior art EPO-producing cell lines that could be fused successfully to lymphoblastoid cells, Green Test., R. Trial Tr. at 427: 10-25.

HMR/TKT urges that Dr. Heartlein did not duplicate Sugimoto and, therefore, that his experiments cannot be used to show that Sugimoto was not enabled. *Johns Hopkins Univ.* v. *CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed."). As pointed out in *Amgen I*, however, the reason Dr. Heartlein did not duplicate Sugimoto was that he could not do so—he could not obtain starting materials that produced EPO at the levels disclosed in the examples of Sugimoto's patent.

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[126] Evidently, Amgen even tried to purchase the starting materials and the hybrid cells directly from Sugimoto's assignee, Hayashibara Company, Ltd. *See* Rathmann Test., R. Trial Tr. at 599: 8-13. While it may be, as HMR/TKT asserts, that Amgen simply did not offer a large enough incentive to retrieve the starting materials, the fact remains that no one skilled in the art was able to obtain them in any manner, i.e., via deposit, financial incentive, or experimentation.

Amgen I, 126 F. Supp. 2d at 109. Therefore, Dr. Heartlein's failed experiments are relevant to the analysis.

HMR/TKT argues that EPO-producing cells such as the human cell line that Goldwasser obtained from Abbott and from the American Type Culture Collection (ATCC) were available to the public and that, as of 1984, several groups of researchers had reported human kidney tumor cells capable of production of human EPO. *See, e.g.*, HMR/TKT's Proposed Findings of Fact ¶¶ 281-85; HMR/TKT's Response to Amgen's Proposed Conclusions of Law and Findings of Fact ¶ 21. The evidence shows, however, that these cells were not comparable to the starting materials reported by Sugimoto. Lin Test., R. Trial Tr. at 562: 19-563: 11 (testifying that Amgen was never successful in obtaining EPO producing human cells or tissue sources). The Abbott cells were normal embryonic kidney cells, not kidney tumor cells, and they did not produce EPO. *Id.* at 541-42; Amgen Project Update, Ex. 234 (providing that Abbott cells did not make EPO). None of the cells Amgen obtained from the ATCC made EPO or could be induced to produce EPO at the levels reported in Sugimoto. Lin Test., R. Trial Tr. at 559: 21-560: 2; 1/20/83 Memo from Browne to Distribution, Ex. 235; Excerpts from Lab Notes, Ex. 236; 3/23/83 Summary Notes from Lin, Ex. 237. As to the other reported EPO producing kidney tumor cells, Dr. Sherwood would not make her cells available, Lin Test., R. Trial Tr. at 540, and Dr. Green testified that none of the cell lines made appreciable amounts of EPO, Green Test., R. Trial Tr. at 421, 471: 6-19, 478: 3-15 (explaining that he was not aware that any of these researchers showed that production of EPO was sustained to the same level over time, and testifying that in 1984, several groups of researchers had reported human kidney tumor cells capable of production of human EPO, but they were "all poor producers of the EPO"); Joseph W. Eschbach, *The History of Renal Anemia (Anemia and Erythropoietin)*, Nephrology 4:279-287 (1998), Ex. 48, at 280 (noting that Lin's invention was a "difficult feat"

because, *inter alia*, "there was no source of erythropoietin mRNA").

While it is true, as HMR/TKT points out, that Sugimoto's method is not limited to starting cells that produce a certain threshold amount of EPO, even HMR/TKT itself was unable to find *any* prior art EPO-producing cell lines that could be fused successfully to lymphoblastoid cells to do as Sugimoto claimed. *Amgen I*, 126 F. Supp. 2d at 109; Green Test., R. Trial Tr. at 421: 18-422: 2; 427: 10-25. Further, HMR/TKT points out that Sugimoto claimed that *any* human cells (and specifically any human kidney tumor cells) capable of producing human erythropoietin could be used in his method. *See, e.g.*, Sugimoto Patent, Ex. 2229, at col. 6: 60-68. Yet no one was successful in finding any starter cells that worked—regardless of their EPO production capabilities. This is significant because enablement must be coextensive with the scope of the claims. *Genentech*, 108 F.3d at 1365; *Plant Genetic Systems*, 315 F.3d at 1339.

Although it is not always necessary to deposit starting materials, *Wands*, 858 F.2d at 736; 35 U.S.C. § 112, deposit is required "[w]here an invention depends on the use of living materials such as microorganisms or cultured cells" and it is "impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure." *Wands*, 858 F.2d at 735; *see* Deposit of Biological Materials for Patent Purposes, 52 Fed. Reg. 34,080, 34,084 (Sept. 9, 1987) (noting that a deposit may be required to satisfy enablement requirements of section 112); *see also Chugai*, 927 F.2d at 1211 (discussing circumstances where a deposit may be required). Here, as Dr. Lodish explained, without access to or adequate disclosure of the starting materials, "one could not begin to repeat [Sugimoto's] experiments." Lodish Test., R. Trial Tr. at 289: 16-290: 18l. Therefore, undue experimentation would necessarily be required. *Genentech*, 108 F.3d at 1366 ("[W]hen there is no

disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required.").

(b) Sugimoto Did Not Teach How To Select EPO-Producing Hybrid Cells

Second, Sugimoto neither deposited his putative "hybrids" nor taught how to select true hybrids. Dr. Green's testimony that the formation of hybrid cells—incorporating the material of two parental nuclei into a single nucleus—is "a rare event," went undisputed. *See* Green Test., R. Trial Tr. at 414: 1-8, 415: 2-9. Because most of the cells in a culture following a fusion event are not true hybrids, use of a selection method to remove all cells which are not hybrids is a very important step. *Id.* at 414-16. Sugimoto did not describe any selection method. As a result, according to Dr. Green, if skilled artisans tried to reproduce his experiments as described, "they would have no benefit of the selective system and therefore the amount of work which would be required might make it impossible for them to succeed in isolating such a hybrid." *Id.* at 422: 21-25; *see also Elan Pharms., Inc.* v. *Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) ("The determination of what level of experimentation is 'undue,' so as to render a disclosure non-enabling, is made from the viewpoint of persons experienced in the field of the invention.").

Although Dr. Green admitted that methods to select hybrid cells were available to those skilled in the art at the time, Green Test., R. Trial Tr. at 423: 14-16, 507, he explained that execution of the methods was not routine, because the methods sometimes worked and sometimes did not, and that without publishing which methods to use and whether they worked, "there's no reason to suppose that you can apply it routinely to any combination of cells and have it work correctly." *Id.* at 425: 3-5; *see id.* at 420: 10-14, 422: 16-25, 424: 19-425: 5, 520: 2-24. According to Dr. Green, this lack

of selection method, along with the fact that Sugimoto neither deposited nor characterized the cells, i.e., proved that they were hybrids, posed great difficulties to one skilled in the art attempting to reproduce the procedure. *Id.* at 425: 22-426: 8.[127]

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[127] Amgen also tried to argue that Sugimoto's failure to confirm hybrid formation or identify what confirmation method was used suggests that Sugimoto is not enabled. Dr. Green, however, agreed with Dr. Kingston that procedures for characterizing the selected cells were well known to those of skill in the art as of 1980-1984. *See, e.g.*, Green Test., R. Trial Tr. at 392: 23-393: 4, 413: 23-416: 22, 507: 11-13; Kingston Test., R. Trial Tr. at 92: 24-93: 16. While the failure to confirm hybridization leads to skepticism about Sugimoto's claims, there was, by contrast with selection methods, no suggestion that carrying out these well-known confirmation techniques was difficult or posed additional problems.

For similar reasons, Amgen's argument that Sugimoto is not enabled because he did not teach how to grow his cells in *in vitro* cell culture fails. *See, e.g.*, Amgen's Post-Trial Br. at 11, 12. Although Dr. Lodish testified on remand that some types of kidney cells are not capable of growth in culture with only routine experimentation, Lodish Test., R. Trial Tr. at 337: 24- 341: 10, he had testified during the first trial that one of ordinary skill in the art as of 1984 could adapt a vertebrate cell line to continuous growth in culture with only routine experimentation, Lodish Test., Trial Tr. at 535-36. Moreover, Amgen points to no evidence or experiments, other than Dr. Lodish's unsubstantiated and contradictory testimony, that undue experimentation would be required to adapt the cells in Sugimoto's patent to grow in culture. *See Bruning* v. *Hirose*, 161 F.3d 681, 686 (Fed. Cir. 1998) ("Conclusory and speculative testimony by . . . expert witnesses will not suffice [to show enablement]."); *cf. Telemac Cellular Corp.* v. *Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001) ("Broad conclusory statements offered by . . . experts are not evidence.").

That Dr. Green did not believe that Sugimoto actually achieved growth in culture as reported does not prove that Sugimoto did not enable the process. As discussed earlier in the context of the enablement of Amgen's patents, it is not necessary that a disclosed invention have actually been made or even actually attempted. *See Donahue*, 766 F.2d at 534; *Chugai*, 927 F.2d at 1213. Instead, "what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the inven

HMR/TKT attempts to rely on Dr. Kingston's testimony to lessen the weight the Court accords Dr. Green's testimony. This attempt is unsuccessful because HMR/TKT points to no testimony by Dr. Kingston addressing selection methods specifically, let alone the potential problems identified by Dr. Green. Furthermore, although the Court has indeed considered both Dr. Kingston's and Dr. Green's testimony regarding the amount of experimentation due, *Elan Pharmaceuticals*, 346 F.3d at 1055 (citing *Enzo*, 188 F.3d at 1373-74), it gives more weight to Dr. Green's testimony, because he is undisputedly the more experienced professional in this specific area. *See, e.g.*, Kingston Test., R. Trial Tr. at 128: 2-8 (agreeing that Dr. Green is a "world-renowned expert on somatic cell fusion" and more expert than Dr. Kingston himself in that area).[128]

Moreover, that these deficiencies were debilitating to those skilled in the art trying to reproduce the procedure, and thus required undue experimentation to be overcome, is supported by HMR/TKT's failed attempt to repeat Sugimoto's process to obtain an EPO-producing hybrid cell. Green Test., R. Trial Tr. at 427: 10-22. Dr. Heartlein could not even obtain a putative hybrid when he used multiple selective markers, which make the job of selection easier. *Id.* at 427: 10-428: 12 (not-

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tion." *Id.* (internal citations omitted). Thus, as to this argument, the evidence fails to prove Amgen's point.

[128] Dr. Kingston defined a person of ordinary skill in the field of molecular and cell biology as someone who had a relevant PhD and roughly two years of experience working in the area. Kingston Test., R. Trial Tr. at 128: 12-14. Sugimoto filed his patent application in 1980. *Id.* at 17-24. Dr. Kingston himself was in the second year of his postdoctoral work in 1983, having received his PhD in 1981. At the time Sugimoto's patent application was filed—the relevant time period for determining whether Sugimoto was enabled—Dr. Kingston was not even considered one skilled in the art. *Plant Genetic Systems*, 315 F.3d at 1340 (stating that enablement is determined as of the effective filing date of the patent); *Hogan*, 559 F.2d at 604 (same).

ing that he tried unsuccessfully with one marker ten times and then with multiple markers twenty-seven separate times, finding no putative hybrids on any occasion). While it is true, as mentioned earlier, that Dr. Heartlein did not exactly duplicate Sugimoto's process, he *could not* for the reasons stated above. Morever, as Dr. Green pointed out, even when he used advanced technology, had even more resources at his disposal than Sugimoto had, and had every incentive to achieve, he could not make any hybrid cells. *Id.* at 430: 3-7. Thus, the evidence shows that undue experimentation would have been required to select a hybrid human kidney tumor/lymphoblastoid cell having the EPO-producing properties reported by Sugimoto. *See Genentech*, 108 F.3d at 1366 ("[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.").

(c) Purification of EPO To Be Used To Treat Anemia Was Claimed But Not Taught, and Prior Art Techniques Were Insufficient

Third, Sugimoto did not enable a purification method. Sugimoto's specification states that "conventional procedures" for purification may be used to purify EPO from the lysate produced in Sugimoto's experiments and can be used "in the prevention and treatment of human diseases such as anaemia." Sugimoto's patent, Ex. 2229, at col. 3: 50-65, col. 3: 66-4: 2. HMR/TKT's experts rendered opinions that an ordinarily skilled artisan, combining procedures of Yanagawa, Chiba, and Erslev, could have purified EPO from serum or cell culture medium. *See, e.g.*, Erslev Test., Trial Tr. at 1751: 15-1754: 3; Robbins Test., Trial Tr. 1984: 7-1987: 5; Matsudaira Test., R. Trial Tr. at 910-14. Notwithstanding this

testimony, the Court is persuaded that one of ordinary skill in the art could not have used the prior art purification methods to purify to substantial homogeneity the EPO produced in tumor cell cultures.

Given the state of the art and the skill level at the time, purification of EPO in the context of the Sugimoto patent was not as simple as it seemed; that is, it was not simply a matter of applying *generic* protein purification procedures already well known in the art to purify EPO produced in tumor cell cultures. *See Wands*, 858 F.2d at 737 (noting that the state of the art and level of skill are factors to be considered in the enablement decision). This Court was not convinced during *Amgen I*—nor is it convinced now—that one of ordinary skill could have used the Yanagawa or Chiba purification methods to purify to substantial homogeneity the EPO produced in the tumor cell cultures. *Amgen I*, 126 F. Supp. 2d at 115 (noting as much in support of the conclusion that HMR/TKT failed to show by clear and convincing evidence that the pharmaceutical compositions claimed in the '933, '080, and '422 patents were rendered obvious by prior art). Dr. Green testified that Sugimoto's claim that other methods can be used to obtain human EPO preparation of high purity was "embarrassing[]" because it was "quite impossible." Green Test., R. Trial Tr. at 505: 6-16. He explained that as a scientist, he had to "examine the basis for Sugimoto's statements," and he found them "very deficient." *Id.* at 506: 5-7; *see Wands*, 858 F.2d at 738 (citing the amount of direction in the patent as one of the factors to consider in determining whether undue experimentation is required). Dr. Bradshaw gave specific examples why Yanagawa's purification method could not be used. He explained that the antibody in Yanagawa was not available and could not be substituted and that Yanagawa used an intermediate that would have denatured the EPO protein, potentially resulting in an incorrectly folded molecule. Bradshaw Test., Trial Tr. at 2717: 22-2718: 18, 2721: 4-21. There is also evidence that HMR/TKT's Dr. Erslev did not

believe that prior art purification methods could easily be combined to purify EPO. Three years after Sugimoto's disclosure, he stated in the book *Hematology* that "[r]eplacement therapy with erythropoietin, the most rational approach to the treatment of the anemia of chronic renal failure, unfortunately still lies in the future." Allan J. Erslev, *Anemia of Chronic Renal Failure*, in Hematology (3rd ed. 1983), Ex. 249, at 422.

Moreover, no one to this day has been reported as being able successfully to purify to homogeneity therapeutically effective human EPO from non-recombinant cells grown in culture, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure. Even HMR/TKT's witnesses, Dr. Matsudaira and Dr. Erslev, admitted this. Matsudaira Test., R. Trial Tr. at 930: 16-23; Erslev Test., Trial Tr. at 1755: 17-1756: 3.[129] As this Court pointed out in *Amgen I*, "in light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling then he would have won that lucrative race." 126 F. Supp. 2d at 108; *see also Genentech*, 108 F.3d at 1367 (concluding undue experimentation was needed based, in part, on the fact that the method was not used to make the claimed product for nearly a year). That Sugimoto's assignee had actually discontinued the project further supports the conclusion that Sugimoto's experiments were not enabling. 9/27/82 Rathmann Memo Memorializing Meeting with Assignee, Ex. 239, at 1 (characterizing the program as inacti-

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[129] Although the Federal Circuit made clear that this fact alone is not sufficient to prove non-enablement, *Amgen II*, 314 F.3d at 1355, it acknowledged that it did have some probative value. Moreover, when analyzing this aspect of the case, the Federal Circuit was under the misunderstanding that Dr. Erslev was Amgen's witness when in actuality he was HMR/TKT's witness. Furthermore, the Court does not rest its decision on this fact alone but also on the many other reasons discussed above.

vated and "dormant").[130] Moreover, the experiments of HMR/TKT's star witness, Dr. Heartlein, affirm that undue experimentation would be required to produce results similar to those reported by Sugimoto. As discussed in *Amgen I*, after many attempts, Dr. Heartlein could not identify any clones producing EPO in fusions involving the HEpG2 cells. As HMR/TKT points out, the Sugimoto patent is not limited to certain types of EPO-producing cells, and, therefore, this failure alone indicates that Sugimoto's patent is not enabled. *Genentech*, 108 F.3d at 1366.[131]

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[130] While this memorandum contains inadmissible hearsay, Fed. R. Evid. 801, it was admitted without objection, *see* R. Trial Tr. at 604-06, and is thus entitled to full probative weight. The confirming testimony to which objection was properly raised, Rathmann Test., R. Trial Tr. at 599: 8-13 (testifying that the assignee had said that the project had been discontinued); *id.* at 602: 8-14 (explaining that the assignee had abandoned the program so he attempted to offer money to try to retrieve some cells), was admitted only for the fact of communication (relevant on the issue of Amgen's ability to obtain the cells) and plays no part in this aspect of the analysis.

[131] In addition, Amgen argues strenuously that there is no evidence that Sugimoto actually accomplished what he claimed, that is, there is no evidence that he purified the EPO or for that matter that the lysate produced from the cells actually contained human EPO—let alone EPO that would have been therapeutically effective. *See, e.g.*, Amgen's Proposed Findings of Fact and Conclusions of Law ¶ 37; Amgen's Post Trial Br. at 12-13; Amgen's Reply to HMR/TKT's Opening Br. at 8; Amgen's Reply to HMR/TKT's Proposed Findings of Fact ¶ 220. In support, Amgen points out that Sugimoto never claims in the specification actually to have purified the EPO, to have made an EPO pharmaceutical composition, or to have administered it to any patient in need of EPO treatment. Sugimoto Patent, Ex. 2229, col. 3: 51-65; Green Test., R. Trial Tr. at 492: 5-12. Indeed, even HMR/TKT's Dr. Heartlein conceded that Sugimoto did not purify what he called EPO and that there was no evidence that Sugimoto's protein was ever formulated into a pharmaceutical composition or that the protein actually would be suitable as a pharmaceutical. Heartlein Test., Trial Tr. at 1820: 22-25; 1821: 7-11; 1824: 20-1825: 3.

The Court agrees that, given the lack of sufficient controls (attested to by various experts) and the reliance only on the Cotes Assay, Sugimoto's

Thus, given the state of the art and the level of skill at the time—proven by testimony about the prior art and subsequent art—Sugimoto's failure to provide any guidance as to what combination of purification techniques is likely to produce substantially homogenous human EPO from Sugimoto's cell extracts that could potentially be used to treat patients means his patent is nothing more than an "invitation" to experiment—and this is simply not sufficient to satisfy the enablement requirement. *Enzo*, 188 F.3d at 1374; *see also Elan Pharmaceuticals*, 346 F.3d at 1055 ("The disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."). The testimony regarding the state of the art up till the time Amgen's patent issued and the experiments performed by Dr. Heartlein show that more than routine experimentation would be required to combine prior art techniques to purify and make EPO that is therapeutically effective in treating human diseases such as anemia.

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entire patent lacks reliable confirmation that he did what he claimed. As discussed earlier in the context of the enablement of Amgen's patent, however, it is not necessary that a disclosed invention actually have been made or even actually attempted. *See Donahue*, 766 F.2d at 534; *Chugai*, 927 F.2d at 1213. Instead, "what is necessary is that [the patentee] provide a disclosure sufficient to enable one skilled in the art to carry out the invention." *Id.* (internal citations omitted). Nothing in the case relied on by Amgen, *In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973), suggests the contrary. *Id.* at 543 (deeming reference insufficient because it stated that attempts to prepare the claimed compounds were not successful); *Donahue*, 766 F.2d at 532 (explaining in that *In re Wiggins* does not support the view that an invention needs to have been actually attempted or made in order to be enabling under section 102(b)). Although in the context of anticipation these arguments may have relevance, *see, e.g.*, *W.L. Gore & Assocs., Inc.* v. *Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983), here, they do not.

(2) Conclusion

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not work. *Genentech*, 108 F.3d at 1366. "While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification," *id.*, expert witnesses for both sides were shocked at the lack of direction and detail in Sugimoto's patent. *See Wands*, 858 F.2d at 738; *Enzo*, 188 F.3d at 1374. Dr. Green called the patent "a parody of a scientific document" because "[i]t has very, very poorly constructed experiments for examples. It has absence of controls or defective controls. It has many ambiguities, or worse, implausible statements that are not justified by any evidence. In short, it is a thoroughly unacceptable document from the scientific point of view . . . ." Green Test., R. Trial Tr. at 401: 8-14; *id.* at 506: 5-7. Dr. Erslev, *HMR/TKT's* expert, was similarly "flabbergasted" by Sugimoto's patent. Erslev Test., Trial Tr. at 1754: 24-1755: 9. Like in *Genentech*, here "the claimed invention is the application of an unpredictable technology in the early stages of development." 108 F.3d at 1367. As such, the specification must provide skilled artisans with "specific and useful teaching" and "supply the novel aspects of an invention." *Id.* at 1368, 1366. It is not sufficient merely to set forth a "plan or invitation for those of skill in the art to experiment" without providing sufficient guidance as to how to reproduce the starting materials, to select the hybrid cells, and then, most importantly, to purify the EPO so that it can be used, as is stated in the specification, to treat human diseases such as anemia. *Enzo*, 188 F.3d at 1374.

Like in *Chugai*, here a substantial discovery is claimed, yet there is no credible evidence that the claimed EPO can be purified and produced by skilled artisans by the disclosed process. Indeed, all evidence—even that from HMR/TKT itself—is to the contrary. *Chugai*, 927 F.2d at 1217 (basing

decision on same criteria).[132] Therefore, this Court concludes that Amgen has proved by a fair preponderance of the evidence that Sugimoto's claims were not adequately enabled. As a consequence, Sugimoto does not anticipate any of the asserted claims of the '422 and '080 patents.

b. *Obviousness:* Does Sugimoto Render Obvious Any of the Asserted Claims of the '422, '080, '698, and '349 Patents?

A patent is invalid under 35 U.S.C. § 103 if the differences between the patented subject matter and the prior art are small enough that the patented subject matter "as a whole" would have been obvious at the time of the invention to a person having ordinary skill in the art. 35 U.S.C. § 103 (2001); *SIBIA Neurosciences, Inc.* v. *Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). Obviousness is determined based on four factual considerations and a set of secondary objective considerations. The factual considerations that are important are (1) the content of the prior art and its scope; (2) the differences that exist between the claimed invention and the

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[132] HMR/TKT makes one last effort to show enablement by arguing that Amgen itself recognized Sugimoto's enablement by identifying Sugimoto as an EPO-producing cell line in its patents. *See, e.g.*, HMR/TKT's Response to Amgen's Proposed Conclusions of Law and Findings of Fact at 10. This argument is baseless. In Amgen's patents and the prosecution history, Amgen merely repeats what Sugimoto *reported* to have done. *See, e.g.*, '933 Patent, Ex. 1, col. 7: 24-35; '933 Patent File History, Ex. 2034, at 237. This type of reporting is part of an inventor's duty to recount assertions in prior art as Dr. Lin testified. Lin Test., R. Trial Tr. at 587: 18-588: 23. Further, that Amgen tried to procure the cells from Sugimoto does not show that Amgen believed Sugimoto's experiments to be successful, but instead that it was trying to obtain the starting materials—if indeed they were obtainable—so that it could attempt to verify that which Sugimoto claims. Lastly, Amgen told the PTO that Sugimoto did not suggest or teach recombinant procedures involving cloning the EPO gene. 10/3/86 Amendment, Ex. 2001, at 250. This last argument therefore fails.

prior art; (3) the level of skill in the prior art (as opposed to that in the claimed invention); and (4) the "objective indicia of non-obviousness." *Yamanouchi Pharm. Co., Ltd.* v. *Danbury Pharm., Inc.*, 231 F.3d 1339, 1342 (Fed. Cir. 2000); *see also Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Ruiz* v. *A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000).

The "objective indicia of non-obviousness," referred to as secondary considerations, include (1) commercial success; (2) copying; (3) long-felt, but unresolved need; (4) the failure of others; (5) commercial success; (6) unexpected result created by claimed inventions; (7) unexpected properties of the claimed inventions; (8) licenses revealing industry respect for the invention; and (9) skepticism of skilled artisans before the invention. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Although they are "but a part of the 'totality of the evidence' that is used to reach the ultimate conclusion of obviousness," *Richardson-Vicks, Inc.* v. *Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997), these secondary considerations are by no means secondary in importance. *Ryko Mfg. Co.* v. *Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991); *Arkie Lures, Inc.* v. *Gene Larew Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997) (emphasizing that the secondary considerations are not secondary). To the contrary, they "can constitute 'highly probative, objective criteria fully capable of serving as a foundation for the legal conclusion of unobviousness.'" *Perkin-Elmer Corp.* v. *Computervision Corp.*, 732 F.2d 888, 895-96 (Fed. Cir. 1984) (quoting *Raytheon Co.* v. *Roper Corp.*, 724 F.2d 951, 961 (Fed. Cir. 1983)). More than that, "secondary considerations may often be the *most probative* and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *Ruiz*, 234 F.3d at 668 (quoting *Stratoflex Inc.* v. *Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)) (internal quotation marks omitted) (emphasis added).

Importantly, the defense of obviousness can be based on a single prior art reference or more than one prior art reference. In other words, if it is shown that it would have been obvious to one skilled in the art to modify the teachings of a reference or combine the teachings of more than one reference to accomplish the claimed invention, then the patent for the claimed invention is invalid. *SIBIA Neurosciences*, 225 F.3d at 1356; *Richardson-Vicks*, 122 F.3d at 1483. To prevail, however, the alleged infringer must meet two requirements. First, it must show a suggestion, teaching or motivation to modify the reference or combine the prior art references. *Yamanouchi*, 231 F.3d at 1341 (citing *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985)); *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (quoting *C.R. Bard, Inc.* v. *M3 Systems Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998)); *Ortho Pharm. Corp.* v. *Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992).[133] This may be inferred from the prior art, from knowledge of one skilled in the art, or from the nature of the problem to be solved. *Brown & Williamson Tobacco*, 229 F.3d at 1125 (citing *Pro-Mold & Tool Co.* v. *Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996)). Broad conclusory statements, standing alone, are insufficient, however. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Instead, evidence of motivation or suggestion to modify a reference or

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[133] The Federal Circuit has stressed the importance of this showing:

> [V]irtually all [inventions] are combinations of old elements. . . . Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. . . . To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Rouffet, 149 F.3d at 1357-58 (internal quotations and citations omitted).

combine it must be "clear and particular." *Dembiczak*, 175 F.3d at 999; *see Brown & Williamson Tobacco*, 229 F.3d at 1125. Second, it must show that one of ordinary skill in the art would reasonably expect that so combining or modifying the prior art references would achieve success. *Id.*

(1) Claim 1 of the '422 Patent and Claims 2-4 of the '080 Patent

HMR/TKT argues that Sugimoto afforded the skilled worker a reasonable expectation of success in obtaining the claimed invention of the asserted claims of the '422 and '080 patents because Sugimoto discloses on its face every specific element of those claims, except for the extra 166th amino acid. HMR/TKT's Reply Br. After Trial at 10. In other words, it urges, that *because* Sugimoto discloses all the elements of the asserted claims, it necessarily shows that those skilled in the art would have had a reasonable expectation of success in practicing Amgen's claimed invention. This, however, erroneously conflates into a single issue what the Federal Circuit has defined as a two-part inquiry. *See, e.g.*, *Brown & Williamson Tobacco*, 229 F.3d at 1124; *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Also, it fails to address the four factors involved in the obviousness inquiry. *Cf. Ruiz*, 234 F.3d at 660, 664 (vacating and remanding district court's judgment for failure to address and make specific findings on the four factors outlined in *Graham*). Although it may appear today, with the benefit of hindsight, that Sugimoto's patent renders the asserted claims of the '080 and '422 patents obvious, as will be explained below, the record shows that at the time Amgen's patents issued there was no reasonable expectation of success in modifying Sugimoto and doing that which Amgen did. Indeed, what Amgen did was anything but obvious when considered in light of the secondary factors. *See Dembiczak*, 175 F.3d at 999 (stressing the importance of "casting the mind back to the time of the invention" and ignoring the "powerful attraction of hindsight-based obviousness").

(a) Scope and Content of the Prior Art/ Differences Between the Claimed Invention and the Prior Art

HMR/TKT contends that Sugimoto alone, along with what was known by those skilled in the art, renders obvious the asserted claims of the '422 and '080 patents. As stated in *Amgen I*, Sugimoto itself "suggested combining its invention with prior art sources relating to both purification and therapeutic delivery." *Amgen I*, 126 F. Supp. 2d at 114 n.29. Thus, there was motivation to combine Sugimoto and prior art to make EPO to treat patients suffering from diseases such as anemia.

The differences between Sugimoto (combined with prior art knowledge) and claim 1 of the '422 patent and the asserted claims of the '080 patent, however, can be summarized easily.

Sugimoto does suggest all that is contained in claim 1 of the '422 patent. Amgen contends that Sugimoto does not disclose "therapeutically effective" because it does not use those words nor describe an increase in hematocrit. While this argument may indeed have merit in an anticipation analysis, where more complete detail and description may be required, it fails here. Sugimoto suggests (if not teaches) EPO that is therapeutically effective when it claims that its EPO is useful in the treatment of patient diseases such as anemia. Sugimoto Patent, Ex. 2229, col. 3: 66-4: 2; *see also* Kingston Test., Trial Tr. at 1227, 1234. Moreover, it is undisputed that Sugimoto claims it produced human EPO in excess of 1000 units/10 (6) cells, a range HMR/TKT asserts, and Amgen does not dispute, to be therapeutically effective. Sugimoto Patent, Ex. 2229, col. 6: 27-39. Amgen argues in defense that Sugimoto does not suggest purification *from mammalian cells grown in culture* specifically. The Federal Circuit made clear in *Amgen II*, however, that when considering obviousness with respect to the '422 and '080 product claims, "a claimed

product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations." *Amgen II*, 314 F.3d at 1354 n.20 (citing *General Electric Co.* v. *Wabash Corp.*, 314 U.S. 364, 373 (1938), and *Cochrane* v. *Badishce Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884)). Therefore, this argument fails.

There are more differences between Sugimoto and the asserted claims of the '080 patent than there are between Sugimoto and claim 1 of the '422 patent. As the Court explained in *Amgen I*, claims 2, 3, and 4 (by dependency) make reference to the mature erythropoietin amino acid sequence of Figure 6, which is unique to and at the heart of Amgen's invention. Sugimoto does not discuss in any way the amino acid sequence of human EPO. HMR/TKT assumes that because Sugimoto discloses human EPO, it necessarily discloses human EPO with either a 165 amino acid sequence or 166 amino acid sequence. HMR/TKT's Reply Br. After Trial at 12. This, however, is not necessarily true. As Amgen points out, Reply to HMR/TKT's Findings of Fact ¶ 149, this Court already found that changes at the C-terminus neither affect the biological activity of the protein nor inhibit proper secretion from the cells. *Amgen I*, 126 F. Supp. 2d at 133 (concluding that the absence of the 166th amino acid is not significant because the absence of the last four amino acids does not substantially change the glycoprotein). Moreover, HMR/TKT does not dispute that EPO fragments, rather than human EPO, can elicit an erythropoietic response in the Cotes bioassay. *See* Jean-Paul Boissel et al., *Erythropoietin Structure-Function Relationships*, 268 J. Biol. Chem. 15883 (1993), Ex. 2302, at 15983-93 (showing that variants of human EPO with internal deletions are biologically active, as measured in bioassays). Thus, simply because human cells were used does not necessarily mean that the sequence was present.

Amgen also claims, correctly, that Sugimoto does not examine the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, a limitation found in claims 2 and 3 of the '080 patent. While this argument supports a finding that Sugimoto does not anticipate these claims, it does not work here in an obviousness inquiry. As discussed above, Sugimoto claimed its EPO was "advantageously useable . . . . in the prevention or treatment of human diseases such as anaemia" Sugimoto Patent, Ex. 2229, at col. 3: 66-4: 2. This necessarily suggests an increase in reticulocytes and red blood cells since, as Dr. Schumacher explained and Amgen did not dispute, these side affects necessarily coincide with therapeutically effective treatment. Schumacher Test., R. Trial Tr. at 824-25.

(b) Level of Ordinary Skill in the Art[134] and Reasonable Expectation of Success

This Court has already found that those skilled in the art at the time Sugimoto patented his invention would not have been able to use Sugimoto—along with knowledge and skill in the art—to select the hybrids or purify the EPO without undue experimentation. HMR/TKT does not suggest that at the time that Amgen made its claims—as opposed to the time that Sugimoto filed its patent—common knowledge in the art about these procedures had advanced. Moreover, there is no

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[134] HMR/TKT contends and Amgen does not dispute that in this action, "a person of ordinarily skill in the art of the patents-in-suit in 1983-84 would have been a scientist with a Ph.D. or M.D. in the biological, biochemical or medical sciences, working in research at the time and having at least two years of post-doctoral research experience in protein production, glycoslyation, and purification, and in the preparation and clinical evaluation of protein-based pharmaceutical compositions for use in human therapy." HMR/TKT's Proposed Conclusions of Law ¶ 80; Amgen's Responsive Conclusions of Law (accepting by not refuting this assertion); *see also* Kingston Test., R. Trial Tr. at 128: 12-14 (agreeing that one skilled in the filed of molecular and cell biology "would be somebody who has a PhD and roughly two years of experience working in the area").

proof on record—aside from that discussed and rejected—that those skilled in the art would have been capable of practicing Sugimoto let alone practicing Amgen's claimed invention based on Sugimoto and general knowledge of skilled artisans. Indeed, there is proof to the contrary. No one has ever purified EPO from non-recombinant cells to substantial homogeneity and all attempts to obtain a therapeutic result had failed. Although a particular reference need not be enabling to be considered in the obviousness inquiry, the asserted combination (here Sugimoto combined with knowledge of one skilled in the art) must provide a reasonable expectation of successfully practicing the claimed invention. *Boehringer Ingelheim Vetmedica, Inc.* v. *Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003); *Yamanouchi*, 231 F.3d at 1343; *Beckman Instruments, Inc.* v. *LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make or use the apparatus or method.").[135] It is with respect to this part of the

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[135] Although both parties agree that the Federal Circuit in *Amgen II* stated that a reference need not be enabling to be considered prior art when analyzing obviousness, they disagree as to the extent that a non-enabled prior art may be considered. Amgen argues that it is only that which the non-enabled art actually teaches that can be considered. *See, e.g.*, Amgen's Reply to HMR/TKT's Proposed Findings of Fact ¶¶ 215, 216 (arguing that "to render obvious the asserted prior art must enable ordinarily skilled artisans to make and use the claimed invention" and citing *Beckman Instruments*, 892 F.2d at 1551 and *In re Payne*, 606 F.2d 303, 314 (C.C.P.A. 1979) in support). HMR/TKT argues, on the other hand, that the Federal Circuit said in *Amgen II* that a non-enabled reference is relevant to the analysis for all the art it "discloses" and, therefore, argues that anything disclosed in the prior art is fair game.

A review of the case law does not provide a definitive answer but indicates that although a reference need not be enabled to be prior art, the reference when combined with other references or common knowledge of ordinarily skilled artisans at the time of the obviousness inquiry should enable the claimed invention, that is, place it in possession of the public.

analysis that HMR/TKT has failed to carry its burden. It has failed to show by clear and convincing evidence that one skilled in the art could practice Amgen's claimed invention with a reasonable expectation of success. Further, the evidence attested to by multiple experts that Sugimoto's experiments lacked sufficient controls, were not confirmed, and were unbelievable suggests that those of ordinary skill in the art would actually not *reasonably* expect that combining Sugimoto with knowledge of skilled artisans would achieve success. *Brown & Williamson Tobacco*, 229 F.3d at 1125.

(c) Secondary Considerations

As discussed in great detail in *Amgen I*, 126 F. Supp. 2d at 115-16, this is definitely a case where the secondary considerations weigh heavily into the Court's decision. Indeed, here they represent the "most probative and cogent evidence in the record." *Ruiz*, 234 F.3d at 668 (quoting *Stratoflex*, 713 F.2d at 1538). Before Amgen's path-breaking invention, there was a long-felt need for the mass production of EPO. *Amgen I*, 126

"If not, every otherwise anticipating reference that is proved to be non-enabling would automatically render the claim obvious, despite not teaching ordinarily skilled artisans how to make and use the invention." Amgen's Reply to HMR/TKT's Proposed Findings of Fact ¶ 216. Arguably, if the non-enabled reference can be combined with other references or knowledge of those skilled in the art such that the combination teaches how to make and use the now claimed invention then it should render the claim obvious. In other words, if by the time the claimed invention is patented, the skill in the art or other references that have been suggested have filled in the missing blanks from the non-enabled reference, then the claimed invention should be rendered obvious. On the other hand, if the missing blanks are still missing (or the non-enabled reference does not suggest the right combination of other references) then the non-enabled reference should not be able to render the claimed invention obvious. In sum, although a prior art reference need not be enabled to render a claimed invention obvious, enablement is not wholly irrelevant. As discussed above, here, the missing blanks were still missing when Amgen filed its patents, and HMR/TKT has not shown a reasonable expectation of success on the part of skilled artisans.

F. Supp. 2d at 108. Many skilled artisans tried unsuccessfully to achieve Dr. Lin's inventions. *Id.* at 115-16. If Sugimoto's invention truly rendered Amgen's invention obvious, one wonders why so many tried and failed. *See Panduit Corp.* v. *Dennison Mfg. Co.*, 774 F.2d 1082, 1099 (Fed. Cir. 1985) ("That many others including [the alleged infringers] had tried for years and failed to create the [claimed invention] is virtually irrefutable evidence that the [claimed invention] would not have been obvious to those skilled in the art when it was invented."), *judgment vacated on other grounds*, 475 U.S. 809 (1986), *on remand*, 810 F.2d 1561 (Fed. Cir. 1987). Importantly, it was Amgen's invention that opened the floodgates for EPO production and led to the first pharmaceutical composition containing EPO to obtain FDA approval. *Amgen I*, 126 F. Supp. 2d at 116. It was Amgen that won the lucrative race to make human EPO suitable for treatment of chronic anemia. *Id.*

HMR/TKT argues, however, that Amgen did not explain to which claims its success was attributable, and that the mapping of the EPO gene was claimed in Dr. Lin's '008 patent. HMR/TKT's Response to Amgen's Proposed Findings of Fact ¶46. In support, it cites *Riverwood International Corp.* v. *Mead Corp.*, 212 F.3d 1365, 1367 (Fed. Cir. 2000) (citing *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)). In *Riverwood* and *GPAC*, however, success was attributable to factors that were entirely outside the scope of the claims. This is not the case here. The evidence suggests that these patents were groundbreaking in their own right since, as discussed above, no one had been able, even using Sugimoto, to purify to homogeneity EPO (as claimed in the '422 patent)[136] or to

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[136] This Court interpreted "purified from mammalian cells grown in culture" to mean purified to substantial homogeneity. *Amgen I*, 126 F. Supp. at 89. It found, however, the evidence was insufficient to warrant the conclusion that plasma EPO could be purified to homogeneity via the prior art. *Id.* at 115.

produce a product that was actually therapeutically effective (as claimed in the '422 and '080 patents).

(2) Claims 4-9 of the '698 Patent and Claims 1, 3, 4, 6, and 7 of the '349 Patent

HMR/TKT contends that every element of the asserted claims of the '698 and '349 patents is found in Sugimoto except the 166th amino acid of Figure 6, the "non-human" or non-EPO promoter or transcription control sequences and the amplified marker DNA. HMR/TKT's Opening Br. After Trial at 41-44. The missing elements, it argues, were available and routinely used in the art in 1983-84. Specifically, it asserts that

> [g]iven the teachings of Sugimoto, it would have been obvious for the ordinary skilled worker to use retroviral insertion to operatively link a retroviral promoter and its transcription control sequences to the erythropoietin production genetic sites in a kidney or liver tumor cell that produced EPO and to transfer those production sites . . . with an amplifiable marker DNA if desired, to a lymphoblastoid cell.

Id. at 41-42. HMR/TKT, however, fails to show a suggestion or motivation to modify the teachings of Sugimoto to create what Amgen claims. Moreover, it has not shown with clear and convincing evidence that one of skill in the art would have had a reasonable expectation of success in achieving Amgen's '349 or '698 claimed inventions using such techniques. Finally, as they did in the context of the '080 and '422 claims, the secondary factors weigh heavily in Amgen's favor on the issue.

(a) Scope and Content of the Prior Art/ Differences Between the Claimed Invention and the Prior Art

Sugimoto differs from the asserted claims of the '349 patent in that it does not disclose the "non-human" or non-

EPO promoter or transcription control sequences as claimed in the asserted claims of the '349 patent. Sugimoto differs from the asserted claims of the '698 patent in that it does not disclose the amino acid sequence of Figure 6,[137] amplified marker DNA, the "dihydrofolate reductase (DHFR) gene DNA," or use of a non-EPO promoter operatively linked to the EPO gene.[138]

With respect to amplified marker DNA, HMR/TKT asserts that Sugimoto's claimed hybrid cells comprise amplified DNA because they have more copies of the EPO gene than are found in normal cells. HMR/TKT Proposed Findings of Fact at 94. Dr. Lodish testified, however, that amplified EPO DNA refers to an increase in the "number of copies of EPO DNA relative to *other* DNA sequences in the genome."

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[137] *See* discussion *supra* regarding Figure 6 and obviousness of the '080 and '422 patents.

[138] HMR/TKT argues that the "non-human" or "other than human" limitations of the asserted patent claims cannot save them from invalidation, because they are source or process limitations. HMR/TKT's Opening Br. After Trial at 42. As HMR/TKT admits, however, there are other "missing elements" from Sugimoto's patent, like transcription control sequences, the amino acid sequence found in Figure 6, amplified marker DNA, the DHFR gene, and operative linkage to the EPO gene. These differences, as will be discussed further below, are determinative notwithstanding the "non-human" or "other than human" limitations. Therefore, the Court declines to address this argument as it relates to these patents. That being said, it is not altogether clear that source or process limitations are irrelevant when considering process claims, as opposed to product claims. *See, e.g.*, *In re Luck*, 476 F.2d 650, 653 (C.C.P.A. 1973) (noting in the product-by-process claim context that process limitations can in certain situations distinguish the product over prior art); *In re Moeller*, 117 F.2d 565, 568 (C.C.P.A. 1941) (same). Moreover, the Federal Circuit did not state that a claimed process could not be rendered patentable solely by the addition of source or process limitations, but instead stated that this was the case for a "claimed product" and a claimed composition. *See Amgen II*, 314 F.3d at 1354 n.20 (making clear that the rule applied to patents that address "a claimed *product*"); *id.* at 1356 (noting that source limitations cannot impart novelty to old compositions).

Lodish Test., R. Trial Tr. at 1099: 25-1100: 1 (emphasis added); *see also* James Darnell, Harvey Lodish & David Baltimore, *Molecular Cell Biology* (1st ed. 1986), Ex. 2394, at 457 ("When mammalian cells are grown in culture, *specific sites* on their DNA can become amplified." (emphasis added)); *id.* at 461 (showing in a diagram that DHFR gene copy numbers increase, but does not depict a change in the chromosome copy numbers). As HMR/TKT admits, Sugimoto's claimed hybrid cells had potentially 4 copies of every gene on every chromosome (two from each parental cell). *See, e.g.*, HMR/TKT's Proposed Findings of Fact at 94; Kingston Test., R. Trial Tr. at 98: 19-99: 5. This does not represent an increase in the relative amount of EPO DNA compared to other DNA sequences.

Notwithstanding this, HMR/TKT argues that Dr. Lodish's testimony regarding amplification supports its argument that Sugimoto's hybrid cells will often have more than four copies of the EPO gene. *See, e.g.*, HMR/TKT's Proposed Findings of Fact at 94 (citing Lodish Test., Trial Tr. at 160: 24-161: 10, 494: 24-495: 3). The Court, however, is not convinced that Dr. Lodish's testimony supports this conclusion. Instead, it appears that in the testimony on which HMR/TKT relies, Dr. Lodish was addressing selection for amplification events using the DHRF gene as a selectable marker—a feature totally missing from Sugimioto.

With respect to the other missing elements, including amplification, HMR/TKT argues that they were available and routinely used in the art in 1983-84. *See, e.g.*, HMR/TKT's Opening Br. After Trial at 41. Instead of focusing on the invention as a whole, however, as required under 35 U.S.C. § 103, HMR/TKT approaches the obviousness inquiry on a piecemeal basis, arguing that the separate elements of Amgen's invention existed in the prior art and, separately, "could" have been done easily. *See, e.g.*, HMR/TKT's Opening Br. at 43-44; HMR/TKT's Proposed Findings of Fact

After Trial at 93-115. "[A]bsent some teaching or suggestion, in the prior art, to combine the elements," however, this is "insufficient." *Arkie Lures*, 119 F.3d at 957; *see also Ruiz*, 234 F.3d at 665; *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosure in the prior art to deprecate the claimed invention."); *Connell* v. *Sears, Roebuck & Co.*, 722 F.2d 1542, 1549 (Fed. Cir. 1983). As the Federal Circuit has explained, "[t]hat all elements of an invention may have been old (the normal situation), or some old and some new, or all new, is however, simply irrelevant. Virtually all inventions are combinations and virtually all are combinations of old elements." *Environmental Designs, Ltd.* v. *Union Oil Co. of California*, 713 F.2d 693, 698 (Fed. Cir. 1983).

HMR/TKT tries to hang its hat on the statements in Sugimoto regarding genetic sites and recombinant techniques. *See* Sugimoto Patent, Ex. 2229, col. 1: 55-2: 3. It argues that Sugimoto's reference to "genetic recombination techniques" suggests combining Sugimoto with retroviral insertion art, that is, that Sugimoto suggested the insertion of non-human transcription control sequences. HMR/TKT's Reply Br. at 13. The Court is not convinced. Sugimoto nowhere suggests using "retroviral insertion" to induce expression of EPO. That the specification specifically defines recombination techniques as those "using DNA ligase, nuclease and DNA polymerase," Sugimoto Patent, Ex. 2229, col. 2: 2-3, argues against interpreting a suggestion of retroviral insertion. Similarly, both Dr. Lodish and Dr. Green testified that an ordinarily skilled artisan reading Sugimoto would not have interpreted the section relied on by HMR/TKT as teaching a way to make cells capable of producing human EPO by recombinant DNA techniques. Lodish Test., R. Trial Tr. at 281: 10-282: 4, 285: 6-23; Green Test., R. Trial Tr. at 405: 19-409: 6. While Dr. Kingston testified that the most commonly used technology to increase expression of the EPO gene in 1983-84 was retroviral insertion, Kingston Test., R.

Trial Tr. at 99: 14-23, when asked how Sugimoto teaches recombinant DNA techniques to increase expression of the EPO coating region, he stated that Sugimoto did so by using "ligases and nucleases and polymerases," *id.* at 104: 14-19—not retroviral insertion.

Moreover, it is not as if "retroviral insertion" was a commonly understood technique that could simply be applied by any skilled artisan in 1983-84. Instead, as Dr. Kingston explained, a skilled artisan would have to rely on many different prior art references to achieve it. *See* Kingston Test., R. Trial Tr. at 99-112 (relying on at least six other references in combination in forming opinion about process of inserting a retrovirus and producing erythropoietin from the resulting cell). That all of these references, save one, were published after Sugimoto's patent issued (after 1983) also supports the conclusion that Sugimoto was not suggesting a combination with retroviral insertion. *See* John M. Coffin, Stephen H. Hughes & Harold E. Varmus, *Retroviruses* (1997), Ex. 2481; Roger D. Cone & Richard C. Mulligan, *High-efficiency Gene Transfer Into Mammalian Cells*, 81 Proc. Nat'l Acad. Sci. 6349 (1984), Ex. 2479; Randal J. Kaufman & Phillip A. Sharp, *Amplification and Expression of Sequences Cotransfected with a Modular Dihydrofolate Reductase Complementary DNA Gene*, 159 J. Molecular Biol. 601 (1982), Ex. 2239; David L. Nelson et al., *Metaphase Chromosome Transfer of Introduced Selectable Markers*, 2 J. Molecular & Applied Genetics 563 (1984), Ex. 2476; Munehisa Ueno et al., *Enhanced Erythropoietin Secretion in Hepatoblastoma Cells in Response to Hypoxia*, 257 Am. J. Physiology C743 (1989), Ex. 2480; John H. Weis et al., *Eukaryotic Chromosome Transfer*, 81 Proc. Nat'l Acad. Sci. 4879 (1984), Ex. 2477.

While the motivation to modify can be found outside the reference itself, *SIBIA Neurosciences*, 225 F.3d at 1358, HMR/TKT has not shown that the knowledge of those skilled in the art or the nature of the problem to be solved suggested

this modification. It is undisputed that the later published retroviral insertion references cited by Dr. Kingston do not refer to Sugimoto or to the expression of EPO or any protein that uses a host cell's gene. *See id.* The only reference that discusses expression of an endogenous gene after insertion of a retrovirus is the Weis article, but that article is not about *increasing* the expression of H-2 antigens as compared to starting cells and did not involve using retroviral insertions to identify cells that produce enhanced amounts of a protein that is either expressed in very small quantities or not at all. Weis et al., *supra*, Ex. 2477, at 4879-83 (identifying that the point of the paper is to transfer the chromosomes to cells of other species). Thus, HMR/TKT has failed to prove the existence of a "clear and particular" suggestion to modify Sugimoto or combine it with prior art so as to produce the asserted claims. *Dembiczak*, 175 F.3d at 999 (noting that while the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability must be "clear and particular"); *id.* (explaining that "[t]he range of sources available does not diminish the requirement for actual evidence" of a motivation or suggestion); *see Brown & Williamson Tobacco*, 229 F.3d at 1125 (same); *SIBIA Neurosciences*, 225 F.3d at 1356 (making clear that the suggestion to combine or modify must be proven, even when a claim of obviousness is based on a single prior art reference); *Rouffet*, 149 F.3d at 1357-58.

HMR/TKT fails to show a suggestion to modify Sugimoto or combine it with prior art with respect to amplification as well. With respect to claims 6, 7, and 8, HMR/TKT merely asserts that although Sugimoto does not disclose or teach a means to position a selection marker such as DHFR next to the EPO gene, it renders this element of the claim obvious because "it was well-known in 1983-84 that the DHFR marker gene can be used to transfer and amplify co-transferred DNA sequences when transfected into CHO cells." HMR/TKT's Proposed Findings of Fact ¶ 448; HMR/TKT's Response to

Amgen's Proposed Findings ¶ 40; HMR/TKT's Reply Br. After Trial at 15. While HMR/TKT may have something with respect to this element, fatally, it neither identified any motivation or suggestion to combine this supposed common knowledge with Sugimoto nor demonstrated how this motivation can be found in the prior art or the problem to be solved. HMR/TKT's Proposed Findings of Fact ¶¶ 448, 452. Given that HMR/TKT shoulders the burden here, this lack of evidence and argument is fatal.

(b) Level of Ordinary Skill in the Art and Reasonable Expectation of Success

Even if one could glean the motivation to modify Sugimoto by applying knowledge in the art to create the claimed invention, HMR/TKT would not prevail here. HMR/TKT has not shown that a skilled artisan would reasonably expect to have succeeded in achieving Dr. Lin's claimed '349 or '698 inventions using such known techniques.[139] As mentioned earlier, HMR/TKT parses elements that comprise one limitation. For example, in its Proposed Findings of Fact, it separates the element "comprising promoter DNA, other than human EPO promoter DNA, operatively linked" from the element "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." In doing so, it fails to recognize the import of the combination of elements. As this Court pointed out in *Amgen I*, in the context of the '349 patent and tumor cell references, the identity of the sequence of the DNA encoding human erythropoietin was critical. *Amgen I*, 126 F. Supp. 2d at 114-15. Without it, an ordinarily skilled artisan would not have been able to hook up transcription control

[139] Indeed, the only experimental evidence on record attempting to do what Dr. Kingston described by way of Sugimoto and the prior art failed. As HMR/TKT put it in its 5/10/00 trial brief, "Amgen's Dr. Browne failed completely when he attempted to transfect cells with viral promoters to increase their production of EPO." Amgen's App. to Mot. for Judgment re '349, Tab E (HMR/TKT's 5/10/00 Trial Br.), at 22.

sequences in a way that caused transcription of the EPO gene, or to obtain cells with the specified structures. *Id.* Like the prior art tumor cell references, Sugimoto does not speak to the genetic characteristics of the cells, and HMR/TKT has not shown during either trial that any knowledge possessed by those of ordinary skill in the art in 1983-84 could fill this gap.[140] *Id.* This reasoning equally applies to the '698 patent's "promoter DNA other than human erythropoietin DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" (claim 4) and "amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" (claims 6 and 9).[141]

Moreover, the Court does not overlook the fact that HMR/TKT's only evidence on this issue comes from testimony by Dr. Kingston, who earlier testified that a person of ordinary skill in the art, applying Dr. Lin's specification—which includes the identification of the EPO gene sequence, splice, donor, and restriction sites, and much more detail than Sugimoto's patent—would not have been able to produce EPO using a cell's endogenous EPO gene. Kingston Test., R. Trial Tr. at 116: 23-117: 24 (testifying that an ordinarily skilled worker could not have taken Lin's teaching to insert randomly a retrovirus into a cell and to obtain an EPO-producing cell with a reasonable likelihood of success). His testimony that ordinarily skilled artisans could have combined Sugimoto with references regarding retroviral insertion

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[140] Importantly, the Weis et al. article, discussed above, studied a gene that had already been cloned, and therefore the researchers were able to confirm the structure of the mouse DNA that had been inserted into hamster cells, using Southern blotting techniques. Weis et al., *supra*, Ex. 2477, at 4881-82, Fig. 3.

[141] This reasoning also applies to claims 5, 7, 8, and 9, as they are dependant on the other claims. *Cf. Fine*, 837 F.2d at 1076 ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious.").

is seemingly incongruous, Kingston Test., R. Trial Tr. at 100: 11-101: 19; 116: 11-16; 117: 15-24, not to mention inconsistent with yet other testimony by the doctor. In the first trial, Dr. Kingston stated that before Dr. Lin cloned the EPO gene, it would not have been obvious for one skilled in the art to do what he did. Kingston Test., Trial Tr. at 1357: 11-1358: 12 (explaining why he retracted yet another inconsistent statement). The Court does not, therefore, lend Dr. Kingston's oscillatory testimony on this issue much weight—especially when considered in light of Dr. Green's and Dr. Lodish's testimony that one skilled in the art, lacking knowledge of EPO's DNA sequence, would not have had a reasonable expectation of successfully making EPO-producing cells by genetic recombination. Green Test., R. Trial Tr. at 406: 17-22; 409: 3-6 (explaining that in order to use any of the recombinant methods mentioned in Sugimoto, "you must know the sequence of the erythropoietin gene and that information . . . did not become available until Dr. Lin's inventions"); Lodish Test., R. Trial Tr. at 285: 21-23. Indeed, Dr. Kingston implicitly admitted the importance of knowing EPO's DNA sequence when he testified that the first step in genetic recombination is to isolate the EPO-neo fragment, which suggests that the gene must first have been cloned. Kingston Test., R. Trial Tr. at 103: 17-104: 18 (using Demonstrative Exhibit TX II W as support for conclusion that Sugimoto teaches this type of genetic recombination); Demonstrative Ex. TX II W.[142]

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[142] HMR/TKT argues as it did with the '080 and '422 patents that the cloning and isolation of EPO is the subject of Lin's original '008 patent, and thus cannot save the patents in issue here. In other words, HMR/TKT argues that because Amgen first reported its discovery of the genetic sequence of EPO in the '008 patent, reference to the genetic sequence can simply be ignored in the obviousness inquiry concerning all other patents. The Court disagrees. First, HMR/TKT offers no legal support for this contention. Second, the genetic sequence of EPO is at the heart of these patents. Simply because the sequence specifically is not a novel addition

Thus, HMR/TKT has failed to prove that skilled artisans, without knowing EPO's DNA sequence, would reasonably expect that combining Sugimoto with prior art references regarding retro viral insertion and knowledge regarding amplification would successfully achieve what Amgen claims.

(c) Secondary Considerations

As with the claims of the '422 and '080 patent, the secondary considerations play a large role in the Court's decision with respect to obviousness. For the reasons discussed above and in *Amgen I*, 126 F. Supp. 2d at 116, the Court finds that the secondary factors strongly counsel it against a finding of obviousness. The real world story in evidence here not only reflects the inadequacy of the prior art, but compels a conclusion of nonobviousness of the claimed inventions in suit. *See Panduit*, 774 F.2d at 1099.

(3) Conclusion

Having considered the scope and content of the prior art references, the differences between such references and the claimed inventions, how one skilled in the art might combine such references in order to make what Amgen claimed, and the objective secondary considerations, the Court concludes the HMR/TKT has failed to persuade the Court by clear and convincing evidence that the asserted claims of the '080, '422, '349, and '698, patents were obvious in light of Sugimoto and the prior art.

B. Goldwasser[143]

1. Background

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as compared to *Amgen's* other patents does not render it obvious in light of *Sugimoto's* patent.

[143] HMR/TKT does not contend that Goldwasser anticipates the asserted claims of the '080, '349, or '698 patents or renders obvious any of the asserted claims of the '698 or '349 patents. *See, e.g.*, HMR/TKT's Opening Br. After Trial [Doc. No. 808] at i.-iii.

a. Overview of Goldwasser

Dr. Goldwasser obtained a preparation of highly purified erythropoietin derived from human urine i.e., it was naturally-occurring EPO. *Amgen I*, 126 F. Supp. 2d at 111.[144] From 1979 to 1981, Drs. Goldwasser and Baron conducted a clinical study in which approximately 10,000 units of the human urinary EPO—in doses of 500 and 1000 units—were administered to three anemic patients. Ex. 2057, at A 196399; Erslev Test., Trial Tr. At 1579; *Amgen I*, 126 F. Supp. 2d at 111. Dr. Goldwasser reported a number of effects in the patients: an increase in reticulocyte count in all three patients, an increase in erythroid cells in the marrow and an increased plasma iron clearance rate in two patients, and an increase in red cell mass in at least one patient. *Id.* Expert testimony by Dr. Erslev explained that these effects are "strong evidence for an increase in the rate of red cell production." *Amgen I*, 126 F. Supp. 2d at 112. Hematocrit levels, however, were unchanged. *Id.* As a result, Dr. Goldwasser admits that his abortive, three-patient trial was a failure. *Id.* at 112.

b. The Court's Holdings in *Amgen I*[145]

(1) Anticipation

In *Amgen I*, the Court held that Dr. Goldwasser's study did not anticipate the asserted claims in the '422 and '080 patents, because the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit, and Dr. Goldwasser admitted that "there was no significant change in hematocrit in any patient" and that the trial was a failure. *Amgen I*, 126 F. Supp. at 112. The Court interpreted Amgen's claims to require a therapeutically effec-

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[144] Dr. Goldwasser's work does not pertain to cells that have been altered by recombinant means. *Amgen I*, 126 F. Supp. 2d at 113.

[145] The history of patents that are no longer at issue is not included below. For that information, *see Amgen I*, 126 F. Supp. 2d at 112-14, and *Amgen II*, 314 F.3d at 1352-53.

tive amount of EPO—one that provides a sustained increase in hematocrit. Thus, it held that Dr. Goldwasser's study "falls far short of anticipating" the pharmaceutical composition claims of the '080 and '422 patents. *Id.* at 112. Because claims 2 and 3 of the '080 patent required actual production of red blood cells as well as reticulocytes, the Court also held that Goldwasser did not anticipate these claims. *Id.* at 112.

Further, the Court pointed to other differences between Goldwasser's study and Amgen's claims. First, the Court stated that Amgen specifically excluded urinary EPO preparations from the scope of the claims by including the claim limitations "non-naturally occurring" and "not isolated from human urine." Thus, it concluded that claims 2 and 3 of the '080 patent do not encompass Goldwasser's urinary EPO treatment. *Id.* at 112. Second, Goldwasser's study does not involve cells that have been altered by recombinant means, and therefore, it held that none of the '349 claims are implicated. *Id.*

(2) Obviousness

The Court held that because Dr. Goldwasser's study was a failure and a person skilled in the art "would not reasonably have expected that Dr. Goldwasser's work would eventually bear fruit," none of Amgen's patents were invalid for obviousness. *Amgen I*, 126 F. Supp 2d at 114. The Court also found, *inter alia*, that HMR/TKT "failed to prove the existence of any suggestion in the prior art to combine [Essers or Goldwasser and Yanagawa or Chiba] so as to produce the pharmaceutical compositions claimed in the . . . '080, and '422 patents." *Id.* It explained that "the fact that no one has ever—then or now—attempted to determine if a pharmaceutical composition comprising human EPO could be made from these cultured prior art cells also informs the Court's decision." *Id.* Therefore, the Court stated that "the contention that these various references could be combined to produce a pharmaceutical composition meeting the limitations of . . .

claim 4 of the '080 patent and claim 1 of the 422 patent is simply unsubstantiated conjecture." *Id.* Lastly, the Court stated that the secondary considerations counseled strongly against a finding of obviousness. Thus, at the close of HMR/TKT's defensive case, the Court granted Amgen's 52(c) motion for judgment of validity with respect to the defense of obviousness.

c. The Federal Circuit's Opinion

HMR/TKT challenged, on appeal, the Court's acceptance of Goldwasser's assertion that his test was a failure in light of the testimony of Dr. Baron, Goldwasser's collaborator. *Amgen II*, 314 F.3d at 1352-3. Dr. Baron reported to the FDA in 1984 that stimulation of erythoid marrow was detected. *Id.* Specifically, HMR/TKT pointed out that the Court failed to look to the specification to define therapeutic effect. The Federal Circuit agreed and stated that the term "therapeutically effective" must be construed in accordance with *Markman* v. *Westview Instruments* before the issue of anticipation and obviousness could be resolved. Therefore, it vacated and remanded for further proceedings with respect to Goldwasser. *Amgen II*, 314 F.3d at 1353.[146]

2. The Claims at Issue

On remand, HMR/TKT argues that Goldwasser anticipates claim 1 of the '422 patent and renders obvious claim 1 of the '422 patent and claims 2-4 of the '080 patent.[147] The relevant claims are as follows:

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[146] As the Court has discussed above, this procedure promotes comity and collegiality among the Federal Circuit and the district courts.

[147] HMR/TKT does not contend that Goldwasser anticipates the asserted claims of the '080, '349, and '698 patents or renders obvious any of the asserted claims of the '698 or '349 patents. *See, e.g.*, HMR/TKT's Opening Br. After Trial at i.-iii.

> *'422 Claim 1*: A pharmaceutical composition comprising a *therapeutically effective amount* of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, where in said erythropoietin is purified from mammalian cells grown in culture.

'422 Patent, Ex. 1, col. 38: 36-41 (emphasis added).

> *'080 Claim 2*: An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

'080 Patent, Ex. 1, col. 38: 39-44.

> *'080 Claim 3*: A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.

'080 Patent, Ex. 1, col. 38: 45-50.

> *'080 Claim 4*: A pharmaceutical composition comprising a *therapeutically effective amount* of an erythropoietin glycoprotein product according to Claim 1, 2 or 3.

'080 Patent, Ex. 1, at col. 38: 51-53 (emphasis added).

3. Discussion

a. Anticipation

(1) Claim 1 of the '422 Patent

Given the Court's construction of the term "therapeutically effective," a critical factor in the anticipation analysis is whether any of the effects elicited by Goldwasser actually, in and of themselves, helped to heal or cure the class of patients

listed in column 33 of the specification.[148] Therefore, the Court will review, in turn, the responses elicited by Goldwasser—and asserted by HMR/TKT to be "therapeutically effective."[149]

(a) Increase in Reticulocytes

HMR/TKT argues that a "therapeutically effective amount" of EPO encompasses an amount that results in an increase in reticulocyte count, whether or not there is an increase in hematocrit, because this increase, in and of itself, helps to heal or cure anemia. *See, e.g.*, HMR/TKT's Proposed Findings of Fact ¶¶ 28-31. In support, it explains that reticulocytes function like normal red blood cells and deliver greater amounts of oxygen to the body's tissues than do older red blood cells. *Id.* The increased oxygen delivery to the tissues, it asserts, "confers health benefits on the patient—it can help to resolve anemia and possibly prevent strokes and heart attacks." *Id.* In support of this contention, it relies mainly on the testimony of Drs. Schumacher and Foster. *Id.*

HMR/TKT overemphasizes the relative significance of reticulocytes in the oxygenation of the body's tissue. Experts

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[148] Amgen also argues that Goldwasser does not disclose the limitation "purified from mammalian cells grown in culture." HMR/TKT argues that this is a source or process limitation that the Federal Circuit specifically pointed out could not save claim 1 from invalidation in an anticipation analysis. The Court need not address the issue since, as will be shown below, the evidence shows that Goldwasser did not disclose EPO that is "therapeutically effective."

[149] HMR/TKT did not argue specifically that an increase in erythroid cells in the marrow signifies a therapeutic response. HMR/TKT's Proposed Findings of Fact at 6-14 (contending that reticulocytes, ferokinetics and erythrocyte-mass change (i.e., red cell mass change) are measures of therapeutic efficacy). Presumably, this is because erythroid marrow stimulation means the marrow is stimulated to raise the reticulocytes. Schumacher Test., R. Trial Tr. at 17-25. Therefore, any argument about erythroid cells in the marrow would necessarily be included in an argument about reticulocytes.

from both sides agree that reticulocytes comprise only one percent of all red blood cells. Schumacher Test., R. Trial Tr. at 829: 18-20; Erslev Test., Trial Tr. at 1685: 5-7. They exist for about three days, whereas *mature* red blood cells exist for 100-120 days. Erslev Test., Trial Tr. at 1684: 21-1685: 7. Moreover, no expert testified that a transitory increase in reticulocytes meaningfully elevates the oxygen levels of the body as a whole. Dr. Schumacher did not testify that a mere increase in reticulocytes increases oxygen supply to these tissues. Instead, she carefully testified that "if you are increasing the oxygen supply," there would be a reduction in the risk of stroke or heart attacks. Schumacher Test., R. Trial Tr. at 813-14 (emphasis added).[150] Both Drs. Erslev and Eschbach testified that reticulocytes are not the accepted reference standard for oxygenation of the body as a whole; that is, recticulocyte counts do not provide direct evidence of the number of red blood cells in circulation and do not always reflect the amount of red blood cells in the body. Erselv Test., Trial Tr. at 1687: 14-1689: 7; Eschbach Test., R. Trial Tr. at 653: 6-14 (stating that the number of circulating red blood cells is determined by the hematocrit).[151] This is because measurements of reticulocytes only reflect the production of red blood cells—not the destruction. Erslev Test., Trial Tr. at 1687: 14-1689: 7; Eschbach Test., R. Trial Tr. at 662-64, 670: 8-10. Reticulocytes do not account for the rate of red cell loss, which could exceed the rate of production. As explained by Dr. Eschbach, reticulocytes may never mature into red

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[150] The Court also notes that HMR/TKT produced no evidence that heart attack or stroke were risks associated with the diseases listed in the specification or that a reduction in the risk of stroke or heart attacks helps to heal or cure the diseased states listed in the specification.

[151] This is consistent with the Court's findings in *Amgen I*, that "[b]y increasing and maintaining the patient's hematocrit to normal or near normal levels, the ability of the patient's blood to provide a steady supply of sufficient oxygen to body tissues can be restored." 126 F. Supp. 2d at 99.

blood cells, because of intervening factors such as iron deficiency, infection, inflamation, blood loss, or rapid red cell destruction. Eschbach Test., R. Trial Tr. at 662-64; 670: 21-25.[152]

Perhaps most telling is the fact that experts from both sides agreed that an increase in reticulocytes is merely an *indication* or "surrogate marker" that a therapeutic effect, i.e., one that actually helps to heal or one that makes the patient feel better, is going to follow. *See, e.g.*, Foster Test., R. Trial Tr. at 965: 3-7 (describing an increase in reticulocytes as a "surrogate marker" of activity and of therapeutic effect); Schumacher Test., R. Trial Tr. at 807: 3-5 (testifying that increase in reticulocytes is "the first indication of a therapeutic response"; *id.* at 813: 3-18 ("[T]he reticulocyte response is the *first response that gives you a clue* that you're getting a response from your therapy . . . the *early harbinger* of the cure or treatment." (emphasis added)); Eschbach Test., R. Trial Tr. at 766: 4-17 (agreeing that an increase in reticulocytes puts a physician "on the lookout for the hematocrit to rise"); *id.* at 660: 22-661: 8, 669: 10-670: 2; Christensen Test., R. Trial Tr. at 1186: 9-24 (testifying that reticulocytes

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[152] Dr. Eschbach illustrated his point with an analogy to a bathtub. Eschbach Test., R. Trial Tr. at 662-64. The Court borrows the analogy to provide background here. Consider a bathtub: the water is the level of hematocrit, the spigot spits out reticulocytes (the early red blood cells), and the drain is the cell destruction or loss. Hematocrit is measured by the amount of red cells produced and by the number of red cells destroyed. In a patient suffering from renal failure, many times the hematocrit drops because red cell destruction exceeds the rate at which red cells are being produced. When EPO stimulation is started, it is as if the spigot has been turned on, increasing the amount of reticulocytes flowing into the tub. Eventually, the tub may start to fill, but there is no guarantee that it will, because the drain is not completely plugged. Iron deficiency, infection, inflammation, or blood loss could prevent the reticulocytes from maturing or could destroy red blood cells. Therefore, simply measuring what is coming out of the spigot and not taking into account what is going down the drain is not sufficient.

are a "marker . . . that the marrow is putting out more blood cells," which "signals that there will ultimately be [a benefit]"); *id.* at 1185: 1-17. That Amgen administered more EPO to those patients that showed an increase in reticulocytes and ferrokinetics and told the FDA that *"[t]he first evidence of a response* to three times weekly . . . administration of EPOGEN® is an increase in the reticulocyte count within ten days," *Physicians' Desk Reference* (56th ed. 2002), Ex. 2497, at 582 (describing Amgen's EPOGEN product) (emphasis added), merely supports the point made by HMR/TKT's own witnesses: an increase in reticulocytes is an indicator or marker that an increase in hematocrit will follow.

The bulk of the testimony indicates that an increase in reticulocytes alone does not help patients feel better. Indeed, HMR/TKT's Dr. Erslev conceded that only by increasing and maintaining hematocrit is the patient able to gain energy and feel better. Erslev Test., Trial Tr. at 1681: 18-1683: 2. Even HMR/TKT's Dr. Foster—a pharmacist arguably not qualified to testify in the area—admitted after a series of direct questions from the Court that an increase in reticulocytes such as that exemplified in Goldwasser would not in and of itself help patients feel better. Foster Test., R. Trial Tr. at 964-66.

HMR/TKT places a great deal of weight on Dr. Ohls' testimony regarding the anemia of prematurity. She testified that an increase in reticulocytes is typically accompanied by an improvement in an infant's overall condition that does not necessarily correspond to an increase in hematocrit, and that clinical signs that an infant is doing better as a result of EPO therapy can occur even with a decrease in hematocrit. Ohls Test., R. Trial Tr. at 1020-21 (noting that conditions like tachycardia, apnea, and poor weight gain improve with an increase in reticulocytes, even if the hematocrit stays the same or decreases); *id.* at 1025. While this testimony may seem at first glance to support HMR/TKT's case on this

point, after a careful review of the testimony of Dr. Ohls and her mentor, Dr. Christensen, it is clear that it does not.

Importantly, Dr. Ohls carefully qualified her testimony by stating that the clinical signs of anemia "*gradually* disappear" after a moderate increase in reticulocytes. *Id.* at 1021: 2-4 (emphasis added); *see also* Christensen Test., R. Trial Tr. at 1185: 1-17 (pointing out that Dr. Ohls said "gradually," and explaining that a rise in reticulocyte count, in and of itself, has "no medical meaning," except to "help you predict that eventually this baby is going to have a hematocrit that is stable"). Dr. Ohls' testimony is further qualified by the biological facts associated with babies and anemia. As Dr. Ohls explained, babies, unlike adults, are constantly growing. As they grow, their blood volume also constantly grows in proportion to their size. Ohls Test., R. Trial Tr. at 1022: 9-21. While, in adults, one can measure the percentage of red blood cells in a sampled blood cell volume to get an accurate reading of hematocrit,[153] in babies, hematocrit is a constantly moving target, because as babies grow their blood volume increases. *Id.*; *see also* Christensen Test., R. Trial Tr. at 1184: 7-15 (noting that an infant's growth rate complicates the measuring of hematocrit). Therefore, even an actual increase in red cell *mass* (versus just an increase in reticulocytes) can result in a constant or even decreased hematocrit. Ohls Test., R. Trial Tr. at 1024.[154] Moreover, Dr. Ohls stated that a neonatologist would use reticulocytes to measure EPO's efficiency—not because it necessarily had a therapeutic effect —but because it "means that the EPO is working to stimulate the bone marrow to make new red blood cells." *Id.* at 1026; *see also id.* at 1029: 20-23 ("But in general, when we treat these babies with EPO they start making new reticulocytes,

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[153] Hematocrit is the ratio of the red-cell mass to the total blood volume.

[154] For an explanatory depiction, see Ohls' Demonstrative Ex. 4.

new red blood cells; they stimulate the circulation, build up the red-cell mass, the hematocrit."). As discussed above, however, just because a person's body is making new red blood cells does not mean that it is doing so fast enough to make up for continuing destruction of red blood cells. Presumably, this is why Dr. Ohls and her peers, in their clinical research, measure the hematocrit, the amount of blood drawn out for laboratory evaluation, and the number of transfusions and the volume of transfusions the babies receive in addition to the reticulocyte count. *Id.* at 1040-41, 1043: 21-24.[155]

The significance of Dr. Ohls' testimony is further diminished by the testimony of her mentor, Dr. Christensen. He stated repeatedly that the reticulocyte count, in and of itself, does not have any effect on the baby and does not help the baby in any way. *Id.* at 1183: 15-22, 1185: 1-17, 1186: 6-24. Instead it is merely a biological indicator that a benefit will ultimately follow. *Id.* Further, he clarified that an infant's growth rate does not invalidate hematocrit as a measure of therapeutic efficacy. *Id.* at 1183: 23-1184: 15. Instead, a physician has to consider the growth factor in infants much like a physician takes into account an adult patient's age, sex,

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[155] Indeed, in the cited studies regarding anemia of prematurity, hematocrit was always measured. Darlene A. Calhoun et al., *Consistent Approaches to Procedures and Practices in Neonatal Hematology*, 27 Clinics in Perinatology 733 (2000), Ex. 252, at 734-35 (basing decision to use transfusions solely on hematocrit); Robin K. Ohls et al., *Effects of Early Erythropoietin Therapy on the Transfusion Requirements of Preterm-Infants Below 1250 Grams Birth Weight: A Multicenter, Randomized, Controlled Trial*, 108 Pediatrics 934 (2001), Ex. 253, at 934 (abstract) (measuring hematocrit and concluding that EPO should not be used in infants under 1250 grams birth weight, because it did not prevent use of transfusions); Robin K. Ohls & Robert D. Christensen, *Recombinant Erythropoietin Compared with Erythrocyte Transfusion in the Treatment of Anemia of Prematurity*, 119 J. Pediatrics 781 (1991), Ex. 2507, at 781 (measuring hematocrit and concluding that EPO offers promise as an alternative to transfusion in neonates with anemia of prematurity).

disease state, etc., in order to understand the meaning of the patient's hematocrit. *Id.* Dr. Christensen made clear that EPO is used to stabilize an infant's hematocrit and to prevent it from falling to a level that would require a transfusion. Christensen Test., R. Trial Tr. at 1189: 23-1190: 4.

In further support of the conclusion that reticulocytes in and of themselves do not help to heal or cure babies suffering from anemia is the fact that a decision whether to transfuse a baby (the goal of using EPO on infants is to avoid the necessity of a transfusion)[156] is never based on reticulocytes alone. *Id.* at 1116-17. Evidently, the reticulocytes can be high and the hematocrit low, and in that situation, the baby will still need the transfusion.

In light of Dr. Christensen's testimony and the other testimony discussed above regarding reticulocytes in adults, Dr. Ohls' testimony is unpersuasive. Although, as Dr. Schumacher testified, "therapeutic response" may be "related to the reticulocytes response," Schumacher Test., R. Trial Tr. at 811: 11-12, the evidence does not show that a reticulocyte response, in and of itself, helps to heal or cure patients suffering from anemia or from any of the other diseases listed in column 33 of the specification.

For these reasons, after a careful review of all the evidence, this Court finds that an increase in reticulocytes alone does not in and of itself help to heal or cure a patient suffering from anemia or any of the diseases listed in the specification.

(b) Increase in Plasma Iron Clearance Rate (i.e., Ferrokinetics)

HMR/TKT next contends that increases in the plasma iron clearance rate are an indication that red blood cell production

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[156] Both Dr. Christensen and Dr. Ohls agreed that the goal of using EPO in infants with anemia prematurity is to avoid transfusions. Ohls Test., R. Trial Tr. at 1027: 7-10; Christensen Test., R. Trial Tr. at 1200: 7-21.

has increased and that there is a therapeutic response to EPO. HMR/TKT's Proposed Findings of Fact ¶ 51.[157] As with reticulocytes, however, HMR/TKT has failed to show that an increase in plasma iron clearance rate is "therapeutically effective."

First, an increase in the plasma iron clearance rate indicates an increase in reticulocytes, but not necessarily an increase in red blood cell mass. As discussed above, there are a number of intervening events, such as cell death and destruction, which preclude one from concluding that the reticulocytes become red blood cells. *See, e.g.*, Eschbach Test., R. Trial Tr. at 670: 3-25 (noting that ferrokinetics only reflect red blood cell production, not destruction); *id.* at 658: 2-8.

Second, Dr. Eschbach testified that ferrokinetic measurements were understood to be a biological effect that did not guarantee that a therapeutic response would follow. Eschbach R. Trial Tr. at 660: 22-661: 8; *id.* at 658: 2-8 ("Ferrokinetics is an investigational tool. It does not . . . tell you anything about therapeutic response.").

Third, Dr. Schumacher admitted that inferences as to the rate of red blood cell production cannot be drawn from the plasma iron disappearance rate without also measuring the plasma iron concentration (serum iron) at the beginning and the end of the trial. Schumacher Test., R. Trial Tr. at 835: 17-836: 9, 837: 4-21; Eschbach Test., R. Trial Tr. at 689: 13-691: 20, 693: 21-25; Allan J. Erslev, *Anemia of Chronic Renal Failure*, in *Hematology* (3rd ed. 1983), Ex. 249, at 399. Although the plasma concentration was measured at the be

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[157] When red blood cells are produced, iron in the blood plasma clears into the bone marrow. Schumacher Test., R. Trial Tr. at 805. The rate of clearance of iron from the plasma is known as the plasma iron clearance rate. *Id.*; Eschbach Test., R. Trial Tr. at 693: 4-11. For further explanation, see Eschbach Test., R. Trial Tr. at 689-91.

ginning of the Goldwasser study, it was not measured at the end. Schumacher Test., R. Trial Tr. at 841: 24-842: 2.

Because HMR/TKT points to no other persuasive evidence on the point,[158] the Court finds that it has failed to prove that an increase in the plasma iron clearance rate, in and of itself, helps to heal or cure anemia or any of the diseases referred to in column 33 of the specification.

(c) Erythrocite (Red Cell) Mass Changes

An increase in erythrocite mass, i.e., an increase in red cell mass, is an increase in the number of erythrocytes. That is, it reflects an increase in the aggregate number of red blood cells. Schumacher Test., R. Trial Tr. at 896: 16-897: 10. HMR/TKT argues that Dr. Eschbach testified that erythrocite mass change is a measure of therapeutic efficacy because increasing the number of red cells helps to heal or cure anemia. HMR/TKT's Findings of Fact at 13. It omits, however, Dr. Eschbach's clear qualification that this is true only if "there's *significant* mass changes." Eschbach Test., R. Trial Tr. at 658: 13-15. He explained that when erythrocyte mass changes are *of sufficient quantity*, they elicit a therapeutic effect because they represent an increase in hematocrit. *Id.* at 660: 1-5.

Here, HMR/TKT does not produce any evidence that the red cell mass changes were significant or meaningful. Indeed, arguably it cannot prove such a thing. Dr. Eschbach's testimony, undisputed by any of the expert witnesses, that a significant increase in erythrocyte mass is the same as an increase in hematocrit prevents HMR/TKT from so proving,

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[158] HMR/TKT has made other arguments in support of its contention, most of which center on the literature. The Court, however, has not found any of these arguments persuasive, given Amgen's more than adequate counter-arguments. *See, e.g.*, HMR/TKT's Proposed Findings of Fact ¶¶ 52-60; Amgen's Response to HMR/TKT's Proposed Findings of Fact ¶¶ 24-29.

because the Court has already found and the Federal Circuit has affirmed that there was no significant increase in hematocrit in any of the patients. Thus, there could be no significant increase in red cell mass.

For that matter, given that the red cell mass changes only occurred in one patient and were not shown to be significant, the evidence does not support a finding that Goldwasser's EPO actually elicited red cell mass increases.[159]

Further, HMR/TKT did not prove that a larger dose of Goldwasser's EPO would have increased red cell mass, increased hematocrit, or elicited a therapeutic response. While there is some evidence in HMR/TKT's favor, the bulk of it suggests the contrary.

First, Dr. Baron himself attempted to increase the dosage and the duration with patient #3, and still there was no recorded increase in hematocrit above the baseline level at any time during or after the study. Indeed, the opposite occurred; as HMR/TKT's expert attested, the patient's red cell mass declined over the treatment period. Goldwasser Data, Ex. 242, at AM 47 038668 (patient #3); Schumacher Test., R. Trial Tr. 885: 14-886: 20; *id.* at 887: 1-5; Eschbach Test., R. Trial Tr. at 759: 6-17 (testifying that there was no significant increase in hematocrit for any of the three patients); 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007 (explaining to the FDA that the third patient received a trial of the medication using an altered protocol that increased the dosage and length of time).[160]

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[159] This is consistent with the Court's finding in *Amgen I* that "actual production of mature red blood cells was not achieved." *Amgen I*, 126 F. Supp. 2d at 112.

[160] HMR/TKT argues that Dr. Baron did not extend the duration long enough, since he only administered the medicine for three weeks. *See, e.g.*, Schmumacher Test., R. Trial Tr. at 894: 13-15. It points to Dr. Baron's letter to the FDA, which stated that "one needs to give larger

Second, although HMR/TKT presented evidence that the experimentors did not believe the EPO was toxic or impure, *see, e.g.*, IND Application for EPO, Ex. 2489, at HMR 935380, 935344; 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007, there is contrary evidence that Goldwasser's EPO was unsuitable for increased dosages. Eschbach Test., R. Trial Tr. at 706: 1-16 (testifying that it was impure and toxic), IND Application for EPO, Ex. 2489, at HMR 935386. Dr. Eschbach even opined that, given these issues with the Goldwasser preparation, the international review boards likely would not have permitted Goldwasser to give more of his urinary EPO preparation to human subjects even had he wanted to, Eschbach Test., R. Trial Tr. at 705: 20-706: 16, and that skilled artisans would likely refrain from giving it to patients in larger dosages for longer duration. *Id.* at 704: 22-23, 705: 22-706: 16; IND Application for EPO, Ex. 2489, at HMR 935386.

Although HRM/TKT's expert, Dr. Schumacher testified that had Goldwasser's EPO been continued in a larger dose, an increase in hematocrit would have been seen, Schumacher Test., R. Trial Tr. at 894: 12-15, Dr. Eschbach testified that the results would not have been different had a larger dose

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doses than initially anticipated and for more prolonged periods of time to achieve the substantial and lasting stimulation of red cell production." 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007. It also points to testimony by Drs. Schumacher and Eschbach and to Amgen's product literature, which claim that a rise in hematocrit usually occurs within two to six weeks. Schumacher Test., R. Trial Tr. at 894: 12-16; Eschbach Test., R. Trial Tr. at 725: 12-21; *Physicians' Desk Reference* (56th ed. 2002), Ex. 2497, at 582. Notwithstanding this, Dr. Eschbach testified that an effective EPO therapy would have produced immediate and dramatic increases in hematocrit. Eschbach Test., R. Trial Tr. at 679: 8-680: 14. Further, even if the Court agreed with HMR/TKT on this specific issue, as discussed above, the evidence simply does not show that an increased dosage would necessarily have lead to therapeutic effectiveness. Here, the red cell mass of the patient that received the altered protocol actually decreased.

been given to the patients over a longer period of time, because of the potential problems with the EPO. Eschbach Test., R. Trial Tr. at 770: 24-771: 6 (explaining that after he received the EPO T ½ values and became aware of the fragments and marked decrease in EPO clearance rate, he doubted whether giving more EPO would make any difference, and believed it might even be harmful); *id.* at 730-31 (same); *id.* at 704-706; *cf.* 2/6/84 Baron Letter to National Center for Drugs and Biologics, Ex. 2058, at A 199034 (describing the increase in reticulocytes as only "mild to modest").

Third, given the incentives to continue the study, the fact that the experimentors themselves chose to abandon it and considered it a failure indicates that an increase in dosage or length of administration would not have led to success. Goldwasser Dep. at 317: 14-321: 2;[161] *cf. Fromson* v. *Advance Offset Plate, Inc.*, 755 F.2d 1549, 1558 (Fed. Cir. 1985) ("[A]nother's experiment, imperfect and never perfected[,] will not serve as an anticipation or as part of the prior art, for it has not served to enrich it." (quoting *Picard* v. *United States Aircraft Corp.*, 128 F.2d 632, 635 (2nd Cir. 1942) (internal quotation marks omitted)).

Thus, HMR/TKT failed to prove that Goldwasser's EPO would have achieved therapeutic effectiveness had Goldwasser continued his experiment. The mere possibility of success is not enough to save HMR/TKT. *Cf. Continental Can Co. USA, Inc.* v. *Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991) (stating in the context of anticipation that "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient," and explaining that the

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[161] HMR/TKT tries to soften the impact of this testimony by arguing that Goldwasser was hired as a consultant by Amgen in 1981. The study, however, was not discontinued until 1988. IND Application for EPO, Ex. 2489, at HMR 935313. Therefore, HMR/TKT has not shown a causal link between the consultancy and the discontinuation.

disclosure must "show that the natural result flowing from the operation as taught would result in the performance of the questioned function").

(2) Conclusion

HMR/TKT contends that all three of the elicited responses discussed above are "surrogate markers of therapeutic efficacy of EPO because each of them represents a critical step in the development of erythroctyes." HMR/TKT's Proposed Findings of Fact ¶¶ 64-66. This specific contention, however, belies its argument. That these three responses are but surrogate markers or indicators that a therapeutic response is on the way necessarily indicates that they did not, in and of themselves, elicit a therapeutic response. This is consistent with this Court's reading of Amgen's specification (discussed in the claim construction part of this memorandum and opinion). These biological responses are critical steps, precursory responses, before a therapeutic result is achieved. Because Goldwasser's study did nothing more than elicit these biological effects or surrogate markers, experts from both sides agreed that there was no evidence that Goldwasser's urinary EPO clinically improved the condition of any of the patients. *See, e.g.*, Means Test., Trial Tr. at 1918: 16-1919: 12 (admitting that there is no evidence that the patients benefitted from any purported activity and labeling the activity as biologic effects); Eschbach Test., R. Trial Test. at 676: 7-18.

In sum, HMR/TKT failed to prove by clear and convincing evidence that Goldwasser anticipates claim 1 of the '422 patent.

b. Obviousness

HMR/TKT argues that Goldwasser alone renders claim 1 of the '422 patent and claims 2-4 of the '080 patent obvious.

(1) Claim 1 of the '422 Patent and Claims 2- 4 of the '080 Patent

(a) Scope and Content of the Prior Art/ Differences Between the Claimed Invention and the Prior Art

Goldwasser differs from claim 1 of the '422 patent in that, as discussed above, it does not disclose EPO that is therapeutically effective or purified from mammalian cells grown in culture. Goldwasser differs from claims 2-4 of the '080 patent in that it does not disclose the mature amino acid sequence of Figure 6[162] or EPO isolated from a source other than human urine.[163] Moreover, claims 2-4 of the '080 patent

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[162] For the significance of this difference, see the discussion of whether Sugimoto renders these claims obviousness.

[163] With respect to "purified from mammalian cells grown in culture" and "not isolated from human urine," the Federal Circuit made clear that a finding of non-obviousness cannot be rendered solely on source or process limitations. *Amgen II*, 314 F.3d at 1354 n.20. Amgen, however, argues not simply that these source or process limitations save the claims in their own right, but that because of these source and process differences, Goldwasser's urinary EPO actually differs in structure and function from Dr. Lin's recombinant EPO because of its source. *See, e.g.*, Amgen's Post-Trial Br. at 33-38. Specifically, it claims that EPO molecules derived from Dr. Lin's cell cultures differ in glycosylation, degradation, clearance rates, in vivo potency, and therapeutic effect. *See, e.g.*, Amgen's Proposed Findings of Fact ¶¶ 69-83. While these differences may be significant, Amgen fails to point to convincing case law recognizing unclaimed product attributes as differences in this part of the analysis. *See, e.g.*, *Graham*, 383 U.S. at 17-18 (noting that an obviousness determination is based in part on differences between the prior art and the "claims"); *Riverwood Int'l Corp.* v. *Mead Corp.*, 212 F.3d 1365, 1366 (Fed. Cir. 2000) (noting that an obvious determination is based in part on "the differences between the prior art and the *claims*" (emphasis added)). That being said, one of the secondary factors recognized by the Federal Circuit is "unexpected properties." *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997) ("[U]nexpected properties can show that a claimed compound that appeared to be obvious on structural grounds was not obvious when looked at as a whole."); *see Rouffet*, 149 F.3d at 1355. Arguably, then, these contentions may be relevant to that part of the analysis. The Court,

require production not just of reticulocytes, but also of red blood cells. Although one patient in Goldwasser showed an increase in red cell mass, the Court has found these increases neither significant nor meaningful—not only because the increases were not substantial enough to increase hematocrit, but also because the results occurred in only one patient. Thus, the Court found, as it did in *Amgen I*, that actual production of mature red blood cells was not evidenced. Lastly, claim 4 of the '080 patent, like claim 1 of the '422 patent, requires therapeutic effectiveness, but the Court has found Goldwasser's EPO is not therapeutically effective.

(b) Level of Ordinary Skill in the Art and Reasonable Expectation of Success

In terms of claim 1 of the '422 patent and claim 4 of the '080 patent, HMR/TKT has not shown that one of ordinary skill in the art had a reasonable expectation of success in obtaining EPO compositions that achieved therapeutic effectiveness. Although HMR/TKT tried to show that it was simply a matter of increasing the length and amount of the dosage, it has not convinced the Court.[164] HMR/TKT provides no other support for its defense.

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however, does not rely on them here, as the many other secondary factors already explicated support a holding of non-obviousness.

[164] Indeed, there is evidence suggesting that it would not have been possible to give increased amounts of the Goldwasser EPO to patients. In a letter to the FDA, Goldwasser made clear that the supply was limited and that preparing more was a painstaking task. 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007; see also 8/17/79 Application for Continuation Grant, Ex. 250, at A 196293 (explaining that the supply of EPO is small and the study was contingent on obtaining more); IND Application for EPO, Ex. 2489, at HMR 935313 (requesting in 1988 that the IND be put on inactive status, as the researchers "do not have sufficient supplies of the drug available to carry on anticipated studies at this time and for the immediate foreseeable future").

With respect to claims 2-3 of the '080 patent, the evidence once again fails to show a reasonable expectation of success in achieving an increase in the production of red blood cells. The one patient that did receive the increased dosages showed a decrease, not an increase, in red blood cell mass. HMR/TKT has produced no further evidence to support its contentions.

(c) Secondary Considerations

Even if HMR/TKT had shown a reasonable expectation of success on the part of one skilled in the art to practice the claimed invention, this Court would still conclude that HMR/TKT has failed to show by clear and convincing evidence that Goldwasser rendered the claims obvious. This is because the secondary considerations counsel strongly against a finding of obviousness, just as they did in the context of Sugimoto. The secondary considerations discussed above with respect to Sugimoto, and explicated in *Amgen I*, apply here. *Amgen I*, 126 F. Supp. 2d at 115-16.

(2) Conclusion

Having considered the scope and content of the prior art, the differences between Goldwasser and the claimed invention, the level of skill in the art, and the objective secondary considerations, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that Goldawsser renders claim 1 of the '422 patent and claims 2-4 of the '080 obvious.

VII. CONCLUSION, DECLARATION, AND ORDER FOR JUDGMENT

As with the first trial, it has been an honor to have presided over this case. The attorneys representing both parties litigated the case with dedication, skill, intelligence, integrity, and patience.

For the reasons set forth above, as a result of the remand trial the Court makes the further declaration:

Claim 1 of the '422 patent is valid.

Claims 2-4 of the '080 patent are valid.

Claims 4-9 of the '698 patent are valid and literally infringed.

Claim 7 of the '349 patent is valid and literally infringed.

SO ORDERED.

/s/ William G. Young
WILLIAM G. YOUNG
CHIEF JUDGE

APPENDIX C

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 97-10814-WGY

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC. and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

MEMORANDUM AND ORDER

YOUNG, C.J. October 30, 2003

INTRODUCTORY NOTE: On September 18, 2003, this Court held that Amgen had successfully rebutted the presumption of prosecution history estoppel but noted that it might have to revisit the issue if the Federal Circuit's *Festo* opinion was published before this Court's opinion was finished. 9/18/03 Pretrial Conference Tr. at 7, ll. 17-25, and 8, ll. 1-5. This Court had scheduled release of this opinion for early October, 2003, pending final proofreading. The Federal Circuit released its opinion in *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, No. Civ.A.95-1066, 2003 WL 22220526 (Fed. Cir. Sept. 26, 2003) ("*Festo III*") on September 26, 2003. Because *Festo III* authoritatively interprets the Supreme Court's decision in *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722 (2002) ("*Festo II*"), the recent Federal Circuit decision governs here under familiar stare decisis principles.

As this Court's interpretation of the Supreme Court decision had proceeded along a somewhat different tack, and

since the growth of the law in this area "moves at a lightning pace," *Festo III*, 2003 WL 22220526, at *11 (Rader, J., concurring), it seems appropriate to set forth this Court's original analysis of *Festo II*, noting its confirmation or remediation on a section-by-section basis by the Federal Circuit in *Festo III*, and identifying and setting forth the revised analysis required by that decision.

As will be discussed in further detail below, this Court reasserts its prior holding—in light of *Festo III*—that Amgen has successfully rebutted the presumption of prosecution history estoppel. Therefore, its earlier finding that HMR/TKT infringes claims 2 through 4 of U.S. Patent No. 5,621,080 (issued April 15, 1997) (the "'080 patent") is reaffirmed.

I. INTRODUCTION

In light of the recent Supreme Court decision in *Festo II*, 535 U.S. 722, the Federal Circuit remanded to this Court its ruling in *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69 (D. Mass. 2001) ("*Amgen I*"), that Amgen, Inc. ("Amgen") was not estopped by the prosecution history from claiming equivalent infringement by the human erythropoietin ("EPO") product ("HMR 4396") produced by Hoechst Marion Roussel, Inc.[1] and Transkaryotic Therapies, Inc. (collectively "HMR/TKT"). *Amgen Inc.* v. *Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1345 (Fed. Cir. 2003) ("*Amgen II*"). Based upon *Festo II*, the Federal Circuit ruled that a presumption of prosecution history estoppel applied here. Therefore, it vacated this Court's finding of equivalent infringement and remanded "for an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel" as laid out in *Festo II. Amgen II*, 314 F.3d at 1345. This opinion addresses the discrete issue of whether Amgen

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[1] Hoechst Marion Roussel, Inc. is now known as Aventis Pharmaceuticals, Inc.

has successfully rebutted the *Festo II* presumption of prosecution history estoppel held to be present in *Amgen II*. *Id.*

II. DISCUSSION

A. Background and Procedural History

In *Amgen I*, this Court construed the amendment "mature erythropoietin amino acid sequence of FIG. 6" in claims 2-4 of U.S. Patent No. 5,621,080 (issued April 15, 1997) (the "'080 patent") as requiring an EPO glycoprotein "comprising the fully realized erythropoietin amino acid sequence of Figure 6, which depicts 166 amino acids." *Amgen I*, 126 F. Supp. 2d at 100. Pursuant to this construction, the Court found that HMR 4396 did not literally infringe claims 2, 3, and 4 of the '080 patent because HMR 4396 comprised only 165 amino acids. *Id.* at 101.

This Court then turned to the doctrine of equivalents and found that HMR 4396 performed substantially the same function in substantially the same way to obtain substantially the same result as the EPO glycoprotein of claims 2 and 3 of the '080 patent. *Id.* at 133. Therefore, it ruled that Amgen's '080 patent was equivalently infringed by TKT/HMR's product. *Id.*

In response to TKT/HMR's argument that Amgen should be estopped from arguing equivalent infringement, this Court ruled that prosecution history estoppel did not apply because Amgen did not add the "mature amino acid sequence of Figure 6" limitation "in an attempt to overcome a rejection, to avoid prior art," but, instead, to "demonstrate that 'same invention' type double patenting did not apply," that is, to distinguish the '080 patent from U.S. Patent No. 5,547,933 (the "'933 patent"). *Id.* at 134-35.

The Federal Circuit agreed that the amendment was made for this purpose but made clear that under *Festo II*, "a narrowing amendment to satisfy *any* requirement of the Patent

Act may give rise to an estoppel." *Amgen II*, 314 F.3d at 1345 (emphasis added). Therefore, it held that the presumption of prosecution history estoppel applied here. The Federal Circuit then vacated this Court's finding of equivalent infringement and remanded for an analysis based on the "narrow ways of rebutting the Supreme Court's presumption of estoppel" outlined in *Festo II*. *Id.* at 1345. Because the Court's factual findings (that TKT/HMR's product performed substantially the same function in substantially the same way to obtain substantially the same result) were not disturbed—or even challenged—on appeal, the Court need only analyze whether Amgen can rebut the presumption of prosecution history estoppel and pursue an infringement claim based on the doctrine of equivalents. If Amgen can, the Court's ruling that Amgen's '080 patent was equivalently infringed shall be reaffirmed.

On May 16, 2003, Amgen moved for judgment under the Federal Rule of Civil Procedure 52(c) that claims 2-4 of the '080 patent are equivalently infringed [Document No. 659]. TKT/HMR opposed Amgen's motion and moved for judgment that Amgen is estopped from asserting infringement under the doctrine of equivalents [Document No. 678].[2] Both parties, however, have agreed that the Court summarily can

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[2] TKT/HMR argues that Amgen should not be allowed to pursue a Rule 52(c) motion because Amgen has already presented evidence on the issue of infringement of claims 2-4 of the '080 patent and a Rule 52(c) motion is a vehicle for a party that has not yet presented its evidence. TKT/HMR's Opp'n [Document No. 703] at 1. Here, when TKT/HMR moved for judgment of non-infringement at the close of Amgen's case, the Court decided in TKT/HMR's favor as to literal infringement but denied the motion under the doctrine of equivalents as to the '080 patent. *Amgen I*, 126 F.Supp. 2d at 101 n.22. Thereafter, TKT/HMR presented its rebuttal case on equivalents. Thus, the proper motion is in actuality one for judgment under Rule 52(a), one which the Court can summarily decide without further evidentiary support.

decide this motion based on the current record without further evidentiary presentation. TKT/HMR's Mem. in Opp'n at 1; Amgen's Mem. in Support at 5-6.

B. Overview Of *Festo II* As Interpreted By This Court And The Federal Circuit

The doctrine of equivalents was created because language is not always sufficiently precise to capture the essence, nuances, and range of an invention in light of unexpected technological advances. *Festo II*, 535 U.S. at 731 ("Things are not made for the sake of words, but words for things." (quoting *Autorigo Co. of America* v. *United States*, 384 F.2d 391, 397 (Ct. Cl. 1967)). The doctrine of equivalents was designed to provide patent applicants the wiggle room that claim language alone cannot, thus protecting patentees from copyists who make insubstantial changes. *Festo II*, 535 U.S. at 732-33; *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 607 (1950). In other words, it was designed to protect the intended invention, even if not adequately or ably described.

Prosecution history estoppel, on the other hand, arises when an amendment, by its language, discernibly limits the scope of the invention before the Patent and Trademark Office (the "Patent Office"). The purpose of prosecution history estoppel is to "hold the inventor to the representations made during the application process and the inferences that may reasonably be drawn from the amendment." *Festo II*, 535 U.S. at 737-39.

> The doctrine of equivalents is premised on language's inability to capture the essence of innovation, but a prior application describing the precise element at issue undercuts that premise. In that instance, the prosecution history has established that the inventor turned his attention to the subject matter in question, knew the

> words for both the broader and narrower claim, and affirmatively chose the latter.

Id. at 734-35. Prosecution history estoppel, therefore, takes root in the virtues of public notice and the reduction of uncertainty that is sometimes created by the doctrine of equivalents. Tony Caliendo, *Foreseeable Trouble: How* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. *Offends Fundamental Policies of the U.S. Patent System by Making Prosecution History Estoppel Depend Upon Foreseeability*, 2003 BYU L. Rev. 309, 314 (2003). Competitors "rely on [prosecution history] estoppel to ensure that their own devices will not be found to infringe by equivalence." *Festo II*, 535 U.S. at 727.

An obvious tension exists between the doctrine of equivalents and prosecution history estoppel. The doctrine of equivalents provides protection for more than just the literal claims, but this added protection creates uncertainty. Caliendo, *supra*, at 314. In other words, competitors are not provided notice of the breadth of the patent. Prosecution history estoppel, on the other hand, can provide such certainty and notice. The Supreme Court in *Festo II* tried to balance the competing interests of public notice and protection of patents by rejecting the Federal Circuit's complete bar approach[3] and further defining which amendments give rise to a presumption of estoppel, what equivalents are subsequently barred by such estoppel, and how the "presumption" of estoppel can be overcome. *Festo II*, 535 U.S. at 736-42.

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[3] In *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 243 F.3d 558, 574-75 (2000) ("*Festo I*"), the Federal Circuit held that prosecution history estoppel completely bars the patent applicant from asserting any equivalent to a narrowed element. This Court previously has followed, but criticized, the Federal Circuit's approach. *See Control Resources, Inc.* v. *Delta Electronics, Inc.*, 133 F. Supp. 2d 121 (D. Mass. 2001).

1. How Does The "Presumption" Work?

   a. *The Court's Original Analysis:* The "presumption" of estoppel is not really a presumption at all, but rather a burden-shifting device similar to the "presumption" of patent validity.

The Supreme Court in *Festo II* made clear that a "presumption" of prosecution history estoppel arises when an amendment is made to secure the patent and the amendment narrows its scope. *Festo II*, 535 U.S. at 736. The "presumption," however, does not completely bar the inventor from asserting infringement against any equivalents to the narrowed element. *Id.* at 738-39. The inventor can overcome the "presumption" by showing that the amendment does not surrender the particular equivalent in question. *Id.* at 740. Thus, this "presumption" shifts to the inventor not only the burden of production but also the burden of persuasion to get out from under the "presumption" of prosecution history estoppel outlined in *Festo II*.[4] Once the patentee meets these

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[4] When dealing with a "true" presumption, if the party with the burden presents evidence to rebut the presumed fact, the presumption simply disappears—the "bursting bubble theory." Young, Pollets & Poreda, Mass. Practice Evidence § 301.3 at 119 (2d ed. 1998). Here, however, the patentee does not simply have to present evidence to rebut the "presumption" but actually has to persuade the Court that it did not surrender the equivalent in question. Such imprecision in language is regrettable, for it means that the definition of the word "presumption" is one thing in patent law and quite another in civil rights and employment discrimination cases. *See, e.g.*, *Reeves* v. *Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 142-43 (2000) (noting that once respondent met its burden of production, the presumption disappeared); *St. Mary's Honor Ctr.* v. *Hicks*, 509 U.S. 502, 510 (1993) (stating that the presumption "simply drops out of the picture" once the defendant has succeeded in carrying its burden of production). Usually such imprecision does little more than confuse the bar and raise the already excessive cost of litigation still higher.

In the area of criminal sentencing, however, the judicial embrace of words like "evidence," "finding," and "fact," has the pernicious effect of cloaking an intellectual vacuity with forms of due process that are wholly

burdens, prosecution history estoppel no longer applies and the patentee may allege equivalent infringement of the narrowed element. *Accord Festo III*, 2003 WL 22220526, at *4.

b. *The Federal Circuit's Analysis:* CONFIRMS THIS COURT'S ANALYSIS.

Neither the Federal Circuit nor the Supreme Court addressed whether the "presumption" outlined in *Festo II* is a true presumption. The Federal Circuit's description of the "presumption," however, confirms this Court's analysis. *Festo III*, 2003 WL 22220526, at *4.

2. What Quantum Of Evidence Is Necessary To Rebut The Presumption?

a. *The Court's Original Analysis:* Proof by a fair preponderance of the evidence is sufficient to rebut a "presumption" of prosecution history estoppel.

While the Supreme Court made clear that the burden of overcoming the "presumption" lies with the patentee, it did not define the quantum of evidence necessary to meet such a burden. In other words, the Supreme Court did not lay out whether the patentee must make a showing by a fair preponderance of the evidence, clear and convincing evidence, or some other standard, nor has any other court yet addressed this quandary in a published opinion.[5]

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unwarranted, thus mistakenly propping up a system that today is both morally and intellectually bankrupt. *See United States* v. *Green*, No. 02-10054-WGY (D. Mass. filed Jan. 10, 2002) (forthcoming).

[5] The Supreme Court did note that the burden here was similar to that outlined in *Warner-Jenkinson Co., Inc.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), and identical to the approach advocated by the United States as Amicus Curiae. *Festo II*, 535 U.S. at 740. Neither of these two sources, however, specify the quantum of evidence required. In *Warner-Jenkinson*, the Supreme Court merely stated that the burden was on the patent holder to establish the reason for an amendment. 520 U.S. at 33.

Important in determining the requisite standard is the surrounding legal landscape. Here, that landscape—patent litigation concerning both the doctrine of prosecution history estoppel and the doctrine of equivalents—is riddled with uncertainty. *Festo II*, 535 U.S. at 732 ("It is true that the doctrine of equivalents renders the scope of patents less certain."). Nevertheless, the Supreme Court purposely preserved the doctrine of equivalents in *Festo II*; it made clear that there was value to the doctrine. *Festo II*, 535 U.S. at 732 ("Each time the [Supreme] Court has considered the doctrine of equivalents, it has acknowledged this uncertainty as the price of ensuring the appropriate incentives for innovation . . . ."); *Warner-Jenkinson*, 520 U.S. at 28 (reaffirming that the doctrine is a secure part of a patentee's settled rights and stating that it was up to Congress—not the Supreme Court—to discard the doctrine). With this landscape in mind, the Court holds that the standard for overcoming the "presumption" of prosecution history estoppel is proof by a fair preponderance of the evidence[6] for the following reasons.

Instituting anything other than the most familiar standard —a fair preponderance of the evidence—would add yet another layer of uncertainty and cause litigation over prosecution history estoppel to proceed inconsistently. *See* John H. Strong, McCormick on Evidence § 340 (5th ed. 1999) (explaining that the clear and convincing standard "has not

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The United States, in its Amicus Curiae brief, urged the Supreme Court to apply a burden comparable to that of *Warner-Jenkinson*, and stated that this burden entailed a "concrete showing." Brief of Amicus Curiae United States at 23, *Festo II*, 535 U.S. 722 (2002) (00-1543).

[6] Proof by a fair preponderance of evidence is proof that shows something to be more likely true than not true. Clear and convincing evidence is "evidence that produces in the mind of the trier of fact an abiding conviction that the truth of the factual contentions are highly probable." Kevin Casey, et al., *Standards of Appellate Review in the Federal Circuit: Substance and Semantics*, 11 Fed. Cir. B.J. 279, 323 (2001) (internal quotations and citations omitted).

become as standardized as is the 'preponderance' formula"); *see also* Kevin Casey, et al., *Standards of Appellate Review in the Federal Circuit: Substance and Semantics*, 11 Fed. Cir. B.J. 279, 323 (2001) (noting that the clear and convincing standard is "not susceptible to precise definition").[7] Such a result is contrary to the purpose of prosecution history estoppel and, therefore, should be avoided.

Moreover, a burden of proof that is too exacting could result, *de facto*, in that which the Supreme Court in *Festo II* was trying to avoid—death of the doctrine of equivalents. *Cf.* Note, *Estopping the Madness at the PTO: Improving Patent Administration Through Prosecution History Estoppel*, 116 Harv. L. Rev. 2164, 2184 (2003) (noting that the Federal Circuit could make the burden of overcoming the presumption more stringent by requiring that patentees produce clear and convincing evidence). Proof by a fair preponderance of the evidence is less exacting than proof by clear and convincing evidence, thereby enabling the "presumption" outlined in *Festo II* to be one that practically can be rebutted—which in turn preserves the doctrine of equivalents. *See* Strong, *supra*, at § 340 (noting that the clear and convincing standard of proof is a "more exacting measure of persuasion" than preponderance of the evidence).[8]

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[7] Of course, there will always be a level of uncertainty in patent law that is inherently case-specific, but this uncertainty is exacerbated by the doctrine of equivalents and would be further exacerbated by an inconsistent application of the standard of proof necessary to rebut the "presumption." See John S. Golian, *Without A Net: The Supreme Court Attempts to Balance Patent Protection and Public Notice in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 36 Creighton L. Rev. 541, 603 (2003) ("[T]he greatest amount of uncertainty is not created by the doctrine itself, but by the court's lack of a consistent application of the rule.").

[8] This burden of proof does not enable the doctrine of equivalents to be applied more broadly than has been its historic scope. *See Warner-Jenkinson*, 520 U.S. at 29 ("[T]he doctrine of equivalents when applied broadly, conflicts with the definitional and public-notice functions of the

Furthermore, the fair preponderance of the evidence standard generally is the one that is applied in patent law. David W. Okey, *Issued Patents and the Standard of Proof: Evidence Clear and Convincing or Merely Ponderous?*, 17 J. Marshall J. Computer & Info. L. 557, 587 (1999). In civil litigation, the clear and convincing standard is saved for special situations in which "a particular type of claim should be disfavored on policy grounds." Strong, *supra*, at § 340. Accordingly, in patent law, it is applied to challenges regarding validity because of the statutory provision found at 35 U.S.C. § 282, that a patent is "presumed" valid. Casey, *supra*, at 324. It is also applied when a patentee claims willful infringement of a patent, *Pall Corp.* v. *Micron Separations, Inc.*, 66 F.3d 1211 (1st Cir. 1995), or violation of the duty of disclosure. Casey, *supra*, at 324. While there are indeed public policy issues implicated in the doctrine of prosecution history estoppel, the "presumption" itself vindicates the public notice function of patent law. Thus, as already noted, to apply an overly exacting standard to a patentee's ability to overcome the "presumption" would unravel the balance the Supreme Court sought between protecting the true scope of a patent and honoring a competitor's reliance on the public record.

Based on this reasoning, the Court holds that the burden of proof most appropriate for overcoming the "presumption" of prosecution history estoppel is proof by a fair preponderance of the evidence.[9]

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statutory claiming requirement."). It ensures that prosecution history estoppel remains tied to its primary purpose without creating either more uncertainty or a complete bar that could eviscerate the doctrine altogether.

[9] During the July 28, 2003, motion hearing, the Court told the litigants that it was inclined to apply this burden of proof and both litigants agreed. 7/28/03 Mot. Hr'g Tr. at 58, ll. 5-8 and 59, ll. 14-21.

b. *The Federal Circuit's Analysis:* DID NOT ADDRESS THIS ISSUE.

Neither the Federal Circuit nor the Supreme Court has discussed the quantum of evidence required to rebut the presumption.

3. What Is The Role Of The Judge And The Jury?

a. *The Court's Original Analysis:* Anomalous as it may seem, the jury plays no role in any of this.

Although it is clear that the equitable doctrine of prosecution history estoppel is for the court to decide, *see, e.g.*, *Pioneer Magnetics, Inc.* v. *Micro Linear Corp.*, 330 F.3d 1352, 1356 (Fed. Cir. 2003); *CAE Screenplates Inc.* v. *Heinrich Fiedler GmbH & Co. KG*, 224 F.3d 1308, 1319 (Fed. Cir. 2000), the Supreme Court in *Festo II* did not provide guidance as to whether the determination that the patentee has rebutted the "presumption" is a question for the court or the jury. Though the bench trial in this case moots the issue here, the question generally remains.

Placing these fact questions before the jury could indeed work against the goals of consistency and predictability since the Federal Circuit would be required to defer to findings of fact made at the trial court level. *See* Raymond G. Areaux and Theodore S. Owers, III, Festo*'s Doctrine of Equivalents: Vitality Reaffirmed in View of New and Old Hurdles*, 48 Loy. L. Rev. 551, 576-78 (2002). On the other hand, determining whether the presumption has been rebutted is not purely technical in nature and involves the kinds of issues—foreseeability, intent, purpose, and reasonableness—normally reserved for a jury. *Cf.* Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 Colum. L. Rev. 1035, 1096-97 (2003) (noting that "juries often decide questions of reasonableness even when facts are not in serious dispute."). Thus, unlike the circumstances in *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 388-

90 (1996), where the Court concluded, with respect to claim construction, that "history and precedent provide no clear answers," here history and precedent do provide answers. These are matters historically resolved by American juries.

For the reasons already expressed in *Control Resources*, however, this Court predicts that litigation over the existence of prosecution history estoppel will be taken from the jury. *But see* Arthur R. Miller, *The Pretrial Rush to Judgment: Are the "Litigation Explosion," "Liability Crisis," and Efficiency Cliches Eroding Our Day in Court and Jury Trial Commitments?*, 78 N.Y.U. L. Rev. 982, 1087 (2003) (criticizing the decision in *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), which embodies this trend in patent law). For the larger implications of marginalizing the jury's historic role, see William G. Young, An Open Letter to United State District Judges, Fed. Lawyer (2003). *See generally* Ellen E. Sward, The Decline of the Civil Jury (2003).

b. *The Federal Circuit's Analysis:* CONFIRMS THIS COURT'S PREDICTION BUT WITH A STRIKINGLY DIFFERENT ANALYSIS.

While the Federal Circuit characterizes the rebuttal question as it relates to the foreseeability criterion as involving mixed fact-law issues, *Festo III*, 2003 WL 22220526, at *5, it treats the issue as one for the district court (not a jury) to decide in the first instance. *Id.* at *4. This can be interpreted to mean that determining whether the "presumption" has been rebutted should be decided by the court because it arises in the context of an equitable defense and involves nuanced questions of mixed fact and law. This is the reading of *Festo III* that makes the most sense. It is fully supported by the cases cited by the Federal Circuit in this portion of the *Festo III* decision. *Id.* at *4 (citing *Loctite Corp.* v. *Ultraseal Ltd.*, 781 F.2d 861, 871 n.7 (Fed. Cir. 1985), *overruled on other grounds by Nobelpharma AB* v. *Implant Innovations, Inc.*, 141 F.3d 1059, 1068 (Fed. Cir. 1998); *Black & Decker, Inc.*

v. *Hoover Serv. Ctr.*, 886 F.2d 1285, 1295 (Fed. Cir. 1989); *Builders Concrete, Inc.* v. *Bremerton Concrete Prods. Co.*, 757 F.2d 255, 258 (Fed. Cir. 1985)). In other words, as the entire concept of prosecution history estoppel is a judicially created equitable doctrine, it makes prefect sense for the district court to do equity in the premises and make the necessarily nuanced fact finding subject to deferential appellate review.

The analysis above comports with prior Federal Circuit decisions and, moreover, is logical and practical.[10] Unfor-

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[10] This approach ensures that *Festo* issues need be addressed only in that small minority of patent cases in which they make a genuine difference. Since under *Dairy Queen, Inc.* v. *Wood*, 369 U.S. 469 (1962), jury issues must constitutionally be first resolved, the normal patent case to be tried to a jury ought proceed roughly as follows: Once the case is sufficiently mature, the court will hold a *Markman* hearing and construe the claims. This done, the court will normally consider a motion for summary judgment. *See, e.g., EMI Group N. Am., Inc.* v. *Intel Corp.*, 157 F.3d 887, 889 (Fed. Cir. 1998).

There are four possible outcomes:

1) The court rules there is no infringement, either literally or under the doctrine of equivalents. The *Festo* issue is gone.

2) The court rules that there is literal infringement. Normally, any lurking *Festo* issue now drops out of the case.

3) The court rules that there is no literal infringement but infringement may exist under the doctrine of equivalents. In this one circumstance, judicial economy may counsel proceeding directly to a *Festo* hearing before the court. If the outcome vitiates the claim under the doctrine of equivalents, the case is over. If, however, upon hearing, the "presumption" appears to have been rebutted, the jury trial will follow and the matter need finally be determined by the court only if the jury finds liability based upon the doctrine of equivalents. If the case is jury-waived, however, the court should decide the matter before determining whether there is infringement under the doctrine of equivalents.

4) There remain genuine issues of material fact concerning literal infringement. In this instance, the best course is to defer any consideration of *Festo* issues until after the jury trial. Not only does the Constitution

tunately, it appears not to be what the Federal Circuit intends—"[T]he determinations concerning whether the presumption of surrender has arisen and whether it has been rebutted are questions *of law* for the court, not a jury, to decide." *Festo III*, 2003 WL 22220526, at *4 (emphasis added). One could hope that the Federal Circuit meant only that the factual issues were reserved for the court given their equitable antecedents and that the phrase "of law" crept in during drafting without much thought. Such comforting yearnings are dashed, however, by the incisive dissent of Judge Newman who points out:

> This court now denies Festo the opportunity to present evidence as to the two criteria of tangentialness and some other reason, establishing these criteria as questions of law, not fact, and decides these questions of first impression without development and without evidence.

Id. at *18 (Newman, J., concurring in part and dissenting in part). In the face of this language, it would strain credulity to conclude that the majority intended something other than pure rulings of law, reviewed de novo on appeal.[11]

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command it, *Dairy Queen*, 369 U.S. at 471-72, it works smoothly. That is, in these circumstances knotty *Festo* issues need never be addressed unless the jury finds liability under the doctrine of equivalents—today, a finding unlikely to be upheld given the stringency with which the Federal Circuit applies this doctrine. *See e.g., Read Corp.* v. *Powerscreen of Am., Inc.* 44 Fed. Appx. 502, 505-10 (Fed. Cir. 2002) (unpublished).

[11] As the intensely fact specific discussion in the text here makes clear, however, this is an unworkable model. Despite the well grounded criticism of *Markman* (see section II.B.3.a), at least claim construction bears a rough analogy to statutory interpretation. Not so here. If these aspects of prosecution history estoppel are transmuted by fiat into pure matter of law reviewable de novo on appeal, every case with an amendment during the prosecution history will require its *Festo* hearing, even more lengthy and involved than the *Markman* hearings of today. This simply will not do.

4. Did The Supreme Court Define One Over-Arching Standard Or Three Distinct Criteria For Rebutting The Presumption?

   a. *The Court's Original Analysis: Festo II* provides one broad, over-arching standard for rebutting the "presumption" of prosecution history estoppel.

While Amgen and TKT/HMR agree that Amgen bears the burden of showing that the "presumption" of prosecution history estoppel is rebutted by a fair preponderance of the evidence, they disagree about what the evidence must show; that is, they interpret the Supreme Court's decision in *Festo II* differently. TKT/HMR asserts that *Festo II* depicts a single rebuttal standard: whether "at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." TKT/HMR's Mem. in Support at 2

Sadly, this is precisely the result predicted in the months before the *Festo III* decision issued:

> Now [I] suppose the [*Festo III*] opinion can come down and say these are all legal, these are all just legal questions. If they do . . . it reminds me of the story of Lincoln, great trial lawyer, he's arguing before a jury and . . . he looks over at the other lawyer and says 'how many legs does a sheep have?' The fellow says it has four. He says, 'now if I call a tail a leg, how many will it have?' And the fellow says it will have five. Lincoln turns to the jury and says 'no it won't, it still will have four. Calling the tail a leg doesn't make it a leg.' [Joseph F. Anderson, Jr., The Lost Art: An Advocate's Guide to Effective Closing Argument 120 (2002) (citing Victoria L. Eslinger's closing argument reciting this incident)].
>
> . . . .
>
> I leave you with what's happening. Because of the complexity, because of the hostility to juries, what in fact you're doing is marginalizing yourselves, diminishing the District Courts, and the law is pretty much in the Federal Circuit.

Remarks of William G. Young, "Festo: Views from the Bench One Year Later" at BIO 2003, July 10, 2003.

(quoting *Festo II*, 535 U.S. at 741.) Amgen, on the other hand, argues that *Festo II* outlines three independent methods (described below) in which to rebut the "presumption" of estoppel. Amgen's Mem. in Opp'n re: '080 [Document No. 716] at 3, 7.

Upon reflection it appears that both parties are partly correct. Amgen is correct in asserting that *Festo II* lays out more than one way in which to rebut the "presumption" of estoppel. *See, e.g.*, *Schwing GmbH* v. *Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1329 (Fed. Cir. 2002) (citing various methods in which to rebut and remanding to the district court); *SoundTube Entertainment, Inc.* v. *Brown Innovations, Inc.*, 233 F. Supp. 2d 188, 196-97 (D. Mass. 2002) (Saris, J.) (applying the various methods of rebutting the presumption); *see also Amgen II*, 314 F.3d at 1345 (referring to *Festo II*'s "narrow ways" of rebuttal and citing the page in *Festo II* that sets out rebutting circumstances) (emphasis added). Indeed, in *Festo II*, the Supreme Court described three situations in which an amendment cannot reasonably be viewed as surrendering the equivalent in question: (1) when the equivalent was unforeseeable; (2) when the rationale underlying the amendment bears no more than a tangential relation to the equivalent in question; or (3) when some other reason exists that suggests that the patentee could not reasonably be expected to have described the insubstantial substitute in question.[12] *Festo II*, 535 U.S. at 740-41.

TKT/HMR, however, is also correct in asserting that the Supreme Court in *Festo II* made clear that to rebut the "presumption" of prosecution history estoppel, a patentee must "show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a

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[12] Amgen argues that TKT/HMR's purported standard is a paraphrase of this third situation. Amgen's Mem. in Opp'n at 3.

claim that would have literally encompassed the alleged equivalent." *Festo II*, 535 U.S. at 741. Upon careful review, it seems that this latter standard is a broad, over-arching one that embraces the three situations described above. When any of the three situations exist, the broad, over-arching standard necessarily is met. In other words, if the equivalent was unforeseeable, it would not have been *reasonable* to *expect* the patentee to have drafted the claim otherwise. Likewise, if the reason for the amendment was only tangentially related to the equivalent, it would not have been *reasonable* to *expect* the patentee to have drafted the claim so that it literally included the equivalent in question; that is, while the patentee perhaps *could have* drafted the claim otherwise to include the equivalent, it would not be *reasonable* to have *expected* it to have done so if the amendment was not even remotely related to the equivalent in question.[13] Finally, the third example simply illustrates that the Supreme Court recognized that the first two rebuttal methods were not exhaustive, that is, that there may yet be another reason why it would be unrea-

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[13] As will be discussed *infra*, it is important to note that the Supreme Court incorporated reasonableness and expectations into the standard. If the question was merely whether the patentee *could* have drafted a claim to encompass the equivalent then the test would simply be a foreseeability test. While some scholars have interpreted the Supreme Court's ruling to collapse the scenarios into one test about foreseeability, *see, e.g.*, Caliendo, *supra*, at 321, this Court declines so to read *Festo II*. If the standard were that simple, the Supreme Court would not specifically have called out the tangential example. Moreover, it would not have injected the notoriously equivocal concepts of "reasonableness" and "expectations" into what could have otherwise been a straightforward standard. *See, e.g.*, C. Alan Fu, *Prosecution History Estopel:* Festo Corp. v. Shoektsu Kinzoku Kogyo Kabushiki Co., 18 Berkeley Tech. L.J. 117, 137 (2003) (noting that the reasonableness test "softens the harsh standard that may be inherent in the foreseeability test" and that it is an "equitable idea").

sonable to expect the patentee to have drafted the claim to have encompassed the alleged equivalent.[14]

This interpretation is also supported by the language of the opinion itself. The Supreme Court, in describing the third rebuttal standard, used the words "some *other* reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question," *Festo II*, 535 U.S. at 741 (emphasis added). In using the words "some other reason," the Supreme Court indicated that the first two methods are merely specific ways to rebut the same broad presumption. Thus, the proper interpretation of the Supreme Court's language is that the first two methods are included within the broad, over-arching standard and the third is that Court's way of recognizing that other circumstances may also suffice to rebut the *Festo II* "presumption." This reading finds further support in the concluding sentence of this section of the opinion, wherein the Supreme Court summarizes the standard: "[t]he patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Id.* The fact that the Supreme Court summarized its analysis in this way suggests that one broad standard encompasses the three situations previously outlined.

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[14] Alternatively, *Festo II* might be interpreted to describe three distinct circumstances under which the "presumption" is rebutted: two specific and one more general. This interpretation is supported by the Federal Circuit's remand to the Court, in *Amgen II*, to interpret if any of the "narrow ways" of rebutting the "presumption" had been met. The Court, however, based on its interpretation of *Festo II* and the subsequent case law, views the three situations not as distinct, but as linked under a single, broad, overarching standard. Yet even if the Court did adopt the alternative interpretation, it would not substantively change this Court's analysis.

Most of the cases that have applied the holdings of *Festo II* also support this interpretation.[15] In *Bosch* v. *Japan Storage Battery Co., Ltd.*, 223 F. Supp. 2d 1159, 1170 (C.D. Cal. 2002), the court listed the three examples that the Supreme Court provided in *Festo II* and then summarized them by stating "[i]n short, '[t]he patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.'"[16] In *Varden Golf Co., Inc.* v. *Karsten Mfg. Corp.*, the court explained that the Supreme Court put the burden of showing that an amendment

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[15] Many of the scholarly articles written since the Supreme Court issued the *Festo II* decision also support this interpretation. *See, e.g.*, Daniel H. Shulman & Donald W. Rupert, *"Vitiating" the Doctrine of Equivalents: A New Patent Law Doctrine*, 12 Fed. Cir. B.J. 457, 462 (2003) ("The Supreme Court held that prosecution history estoppel would apply to additional subject matter not expressly relinquished if the patentee could have drafted a claim to cover the additional subject matter, but did not. The Supreme Court identified a number of reasons why a patentee might not have been able to draft such a claim."); John S. Golian, *supra*, at 543 ("The Court held that in order to rebut this presumption, a patentee must show that the amendment did not surrender a particular equivalent by demonstrating that 'one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.'"); *Leading Cases*, 116 Harv. L. Rev. 402, 407, 410 n.73 (2002) [hereinafter "*Leading Cases*"] (stating that the "the patentee may rebut the presumption by demonstrating that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent," outlining the two specific examples and noting that the Supreme Court "plainly did not intend these examples to be exclusive, adding that 'some other reason' may suffice to rebut the presumption of estoppel") (internal citations and quotations omitted).

[16] It should be noted, however, that in its analysis of the case, the California district court considered first whether the amendment was tangential and next whether it met the over-arching standard. It then concluded, based on the facts, that the patentee had failed to demonstrate both. *Bosch*, 223 F. Supp. 2d at 1172.

has not surrendered a particular equivalent on the patentee and implicitly indicated that this burden was "show[ing] at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Varden Gulf*, 2002 WL 1424567, at *4 (N.D. Ill. 2002). Later, when describing specific cases in which this burden was met, it stated that the Supreme Court's foreseeability example met the broad over-arching standard: "If for example the equivalent was unforeseeable at the time of the application, then the patentee could not reasonably be expected to have described the insubstantial substitute in question." *Id.* at *4; *see also Soundtube*, 233 F. Supp. 2d at 197 (summarizing the patentee's argument as "[the patentee] could not have foreseen the SoundTube system during the prosecution of the patent *and thus* 'one skilled in the art could not reasonably have been expected to draft claim limitations to literally encompass' the SoundTube devices") (emphasis added); *Glaxo Wellcom Inc.*, v. *IMPAX Labs Inc.*, 220 F. Supp. 2d. 1089, 1093 (N.D. Cal. 2002) (summarizing the standard as a single broad, over-arching standard); *ConMed Corp.* v. *Ludlow Corp.*, 235 F. Supp. 2d 109, 122 (N.D.N.Y. 2002) (applying the broad, over-arching standard and concluding that the patentee failed to meet its burden); *SmithKline Beecham Corp.* v. *Excel Pharms, Inc.*, 214 F. Supp. 2d 581, 591 (E.D. Va. 2002) (stating that, to meet its burden, the patentee must satisfy the broad, over-arching standard); *but see Schwing GmbH* 305 F.3d at 1329 (stating that the Supreme Court "discussed several ways in which the patentee could overcome [the] presumption" and listing the three examples from *Festo II* without connecting them to a single, broad, over-arching standard).

Thus, this Court interprets *Festo II* as providing a single standard—albeit a difficult one to satisfy—to determine whether the "presumption" of estoppel has been overcome

and as offering three situations in which the articulated standard would be satisfied.

b. *The Federal Circuit's Analysis:* DIFFERS FROM THIS COURT'S ANALYSIS BUT DOES NOT CHANGE THIS COURT'S ULTIMATE HOLDING.

The Federal Circuit holds that there are three separate "criteria" which the patentee may meet to rebut the "presumption." *Festo III*, 2003 WL 22220526, at *2, *5-*6 ("Specifically, the Court enumerated the three ways in which the patentee may overcome the presumption."). As mentioned above, whether the standard is viewed as three separate criteria or as one over-arching standard, will not, in most cases, change the end-result because the three criteria work in tandem with what this Court viewed as the over-arching standard. In other words, if the equivalent was unforeseeable, or if the reason for the amendment was no more than tangentially related to the equivalent, it would not have been *reasonable* to *expect* the patentee to have drafted the claim to have literally encompassed the equivalent.

The Federal Circuit's interpretation nevertheless may make a significant difference in the outcome of cases because it states that the third—the "some other reason"—criterion is to be narrowly construed. *Id.* at *5. Aside from stating that "a patentee may not rely on the third rebuttal criterion if the alleged equivalent is in the prior art . . . ." and that the "shortcomings of language" may satisfy the criterion, the Federal Circuit left to another day further exposition of this third criterion. *Id.* at *6.

5. What Type Of Evidence May Be Used To Rebut The Presumption?

   a. *The Court's Original Analysis:* Extrinsic evidence may be considered if it does not contradict the intrinsic evidence.

Although the rebuttal standard is narrow, the inquiry and analysis to determine if it has been met is in some respects intricate and, therefore, requires resort to extrinsic evidence. The Supreme Court made clear in *Festo II* that a court must examine the subject matter surrendered by the amendment and the reasonable inferences that can be drawn from the amendment. *Festo II*, 535 U.S. at 737-38; *Schwing GmbH*, 305 F.3d at 1329; *Bosch*, 223 F. Supp. 2d at 1170. This examination is more than a peripheral one.

> There is no reason why a narrowing amendment should be deemed to relinquish equivalents unforeseeable at the time of the amendment and beyond a *fair interpretation of what was surrendered.* Nor is there any call to foreclose claims of equivalence for aspects of the invention that have only a peripheral relation *to the reason the amendment was submitted.*

Festo II, 535 U.S. at 738 (emphasis added). To determine what was fairly surrendered by the amendment, the Court needs to, in many instances, understand the rationale for the amendment. *Id.* Knowing simply that an amendment was made for reasons related to patentability is not enough. The Court needs to understand more specifically why the exact words or limitations were added or deleted and such an understanding is not always immediately evident in the prosecution history. Often patentees change certain aspects of claims in response to an objection. Other times, such as in the case before the Court, patentees voluntarily make changes even when there is neither a Patent Office objection nor rejection and when no prior art threatens the validity of the

invention. Given that the "remarks" that accompany the amendments are cursory at best, in the latter case it is even more difficult to discern the particular rationale for the amendment based on the prosecution history. *Amgen I*, 126 F. Supp. 2d at 135 ("This search for purpose is made more difficult where, as here, there is nothing in the file wrapper as of the date of the amendment indicating that the claims were objectionable to the Patent Office."). Moreover, the "state-of-the-art" at the time of the amendment (a key piece of information necessary to determine foreseeability) generally is not something addressed in the prosecution history—nor are the intricacies of the technology always clear. Therefore, there are instances in which reliance on the prosecution history alone would not inform the court in sufficient detail as to why certain additions and deletions to the claims were made.

Notwithstanding these concerns, TKT/HMR relies on *Pioneer Magnetics* to argue that only the public prosecution history record can be used to demonstrate the purpose of the amendment and that the Court should not consider any extrinsic evidence in determining whether the rationale for the amendment has no more than a tangential relation to the equivalent in question.

TKT/HMR's argument is unavailing here. First, *Pioneer Magnetics* is distinguishable from the instant case. In *Pioneer Magnetics*, when the Federal Circuit stated that only the public record could be used to determine the purpose for the amendment, the court was evaluating whether the amendment was made for patentability reasons (a determination made prior to the assessment of whether the "presumption" of prosecution history estoppel has been overcome). *Pioneer Magnetics*, 330 F.3d at 1356. Thus, this holding is inapposite to the analysis that occurs *after* the court has decided that the amendment was a narrowing one made for patentability reasons and that the "presumption" therefore applies.

Second, neither *Pioneer* nor *Festo II* foreclose the use of extrinsic evidence once the "presumption" of estoppel has been triggered and the patentee is trying to rebut it. *See, e.g.*, Areaux & Owers, *supra*, at 574 (noting that the Supreme Court did not offer any guidance as to whether intrinsic or extrinsic evidence can be used). Moreover, in explaining that the interpretation of the patent *begins*—but does not end—with the literal claims and the prosecution history, *Festo II* apparently gave the patentee leeway to rely on extrinsic evidence to prove that "one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo II*, 535 U.S. at 741; *but see* Pavan K. Argarwal, *Patenting in Line with the Federal Circuit*, 12 Fed. Cir. B.J. 395, 413-14 (2003) ("[W]ith the notice function that the Supreme Court previously announced in *Warner-Jenkinson Co.* v. *Hilton Davis Chemical Co.*, it would seem appropriate to limit the patentee to the public record of the prosecution as the en banc Federal Circuit decided in *Festo*.").

Third, the United States Amicus Brief—relied on by the Supreme Court to define the rebuttable "presumption"—argued that extrinsic evidence can be used that explains but does not contradict intrinsic evidence. Brief of Amicus Curiae United States at 23, *Festo II*, 535 U.S. 722 (2002); Areaux & Owers, *supra*, at 575-6 (noting that the U.S. Amicus Brief was a clue to what type of evidence the Federal Circuit will allow). Moreover, it specifically urged that facts should be drawn from the specific technology involved. Brief of Amicus Curiae United States at 23 n.4. Even the Federal Circuit in *Festo I* (which stated that use of extrinsic evidence would undermine the public notice function) explained that a district court can properly consider any argument made by an attorney that is supported by the prosecution history record. *Festo I*, 243 F.3d at 586 n.6.

Lastly, common sense dictates that extrinsic evidence may be necessary to meet the rebuttal requirements outlined in

Festo II. For example, the prosecution history alone would not show whether an invention, discovery, or technique was foreseeable, or whether a person skilled in the art could have drafted the claim differently. *See, e.g.*, Areaux & Owens, *supra*, at 575 ("[I]t seems plain that evidence of foreseeability will not reside in the prosecution history."). Furthermore, it is the prosecution history itself that triggers the "presumption" of estoppel; thus, if the patentee is limited to the prosecution history in its efforts to rebut that "presumption," it would likely never be successful. Like a standard of proof that is too exacting, limiting the patentee to the intrinsic record would in essence create a result similar to the complete bar the Supreme Court overruled in *Festo II.*

For these reasons, in determining whether Amgen has rebutted the "presumption" of estoppel, the Court will examine the prosecution history in light of the presentations made during the trial and in the parties' submissions. *Cf. Canton Bio-Medical, Inc.* v. *Integrated Liner Tech., Inc.*, 19 F. Supp. 2d 22, 32 (N.D.N.Y. 1998) (relying in part on expert opinion to determine what was surrendered with the amendment and holding that "[a]fter considering the arguments of the parties, their briefing and submissions, the entire relevant record, and the applicable law, the [c]ourt finds that the Defendant's accused process does not infringe the Plaintiff's [] patent, as a matter of law, based on the application of prosecution history estoppel . . . .").[17]

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[17] This case along with other cases predating *Festo II* support the Court's reference to extrinsic evidence. At least one other federal court has relied on extrinsic evidence to aid the analysis. *See, e.g., Envirco Corp.* v. *Clestra Cleanroom Inc.*, 1998 WL 809369, at *3 (N.D.N.Y. Nov. 4, 1998) (noting that determining prosecution history estoppel is based on the patent, specification, and the prosecution history, but if the court requires extrinsic evidence to construe the claims, it may rely on dictionaries, treatises, and, if needed, expert opinion), *vacated on other grounds by Envirco Corp.* v. *Clestra Cleanroom Inc.*, 209 F.3d 1360 (Fed. Cir. 2000).

In other words, the Court will consider extrinsic evidence. It will do so, however, only when that evidence does not *contradict* the intrinsic evidence—the patent, the specification, and the prosecution history. Such an examination thus cannot dissuade the Court from giving the public record its due weight—a significant policy on which patent law is based. Moreover, the Court will not go so far as to consider the subjective intent of the patentees when such intent is not expressed in or supported by the patent or file wrapper. "Such testimony cannot guide the court to the proper interpretation when the patent documents themselves do so clearly." *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996). When, however, such intent is supported by the prosecution history, the Court will consider it because "a full understanding of what the inventors actually invented and intended to envelop with the claim" guides a court to the proper interpretation. *Renishaw PLC.* v. *Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) (discussing claim construction). These limitations on the Court's consideration of extrinsic evidence strike the proper balance between supporting the notice functions of the patenting process and protecting the true scope of an inventor's patent despite the ineptness of language to do so on its own.[18]

b. *The Federal Circuit's Analysis:* RESTRICTS THIS COURT'S APPROACH

The Federal Circuit adopts a more restrictive approach to extrinsic evidence than that set out above. *Festo III*, 2003 WL 22220526, at *5-6. Both this Court and the Federal Circuit interpret *Festo II* as allowing consideration of extrinsic evidence when determining whether the first criterion, fore-

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[18] Although the Court holds that consideration of extrinsic evidence is necessary adequately to determine whether the rebuttal standard laid out in *Festo II* has been met, it recognizes that such consideration, along with other patent law analyses like *Markman*, blur the line between the role of judge and jury. *See* section II.C.3, *supra*.

seeability, has been met. *Id.* The Federal Circuit, however, clearly limits the determination under the second criterion, tangentiality, to intrinsic evidence and strongly suggests that the third criterion should be limited in the same way.[19] *Id.* This is the crucial difference between its analysis and that of this Court. Notwithstanding the revisions necessary to comport with the Federal Circuit's analysis, the Court's holding that Amgen has rebutted the presumption has not changed. The basis for this holding, however, rests on different criteria, as will be explained below.

6. Should Foreseeability Be Analyzed At The Time Of The Amendment Or The Time Of The Original Patent Application?[20]

a. *The Court's Original Analysis:* Foreseeability Should Be Analyzed At The Time Of The Amendment

Some scholars and courts have indicated that the Supreme Court was not clear whether foreseeability should be analyzed at the time of the amendment or at the time of the application. *See, e.g.*, Caliendo, *supra*, at 321; Fu, *supra*, at 134 (noting that the Supreme Court was unclear with respect to when the foreseeability test should be applied).

This Court, however, holds that *Festo II* defined the relevant time period as the time of the amendment, not the time

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[19] The Federal Circuit did not completely rule out resort to extrinsic evidence in determining the third criterion. It stated that intrinsic evidence should be used "when at all possible" and that it "need not decide now what evidence outside the prosecution history record, if any, should be considered in determining if a patentee has met its burden under this third rebuttal criterion." *Festo III*, 2003 WL 22220526, at *6. In *Festo III*, the issue was not squarely before the Court as it is here.

[20] The parties disagree about whether foreseeability, the first criterion, should be analyzed with respect to what was known by those skilled in the art at the time of the original patent *application* or at the time the narrowing *amendment* was made.

of the patent application. First, in *Festo II* the Supreme Court explicitly stated twice that the relevant time period is the time of the amendment. When it first explains why a narrowing amendment should not be deemed to relinquish all equivalents, it considers foreseeability based upon what was known at the time of the amendment. *Festo II*, 535 U.S. at 738. Later, when it summarizes the holding of *Festo II*, the Federal Circuit again states that the "presumption" may be rebutted when the patentee "show[s] that at the *time of the amendment* one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Id.* at 741 (emphasis added). Although the Supreme Court used the word "application" in describing the foreseeability test at one point, *see Festo II*, 535 U.S. at 740 ("The equivalent may have been unforeseeable at the time of the application . . . ."), the Court was referring to the application process, not the time at which the application was originally filed. *Cf. Johnson & Johnston Assoc. Inc.* v. *R.E. Serv. Co.*, 285 F.3d 1046, 1059 (Fed. Cir. 2002) (Rader, J., concurring) ("In reaching this result, the court suggested that if variation had been unforeseeable during the application process, the doctrine of equivalents would still have been available to the patentee.").

Second, the Federal Circuit and other federal courts have also interpreted the relevant time reference to be the time of the amendment (not the time of the application). *See, e.g.*, *Pioneer Magnetics*, 330 F.3d at 1357 (analyzing foreseeability based on what was known at the time of the amendment); *SmithKline*, 214 F. Supp. 2d at 592 (same); *Masco Corp.* v. *United States*, 56 Fed. Cl. 400, 412 n.11 (2003) (noting that there is some support for interpreting *Festo II* as requiring unforeseeability at the time of the amendment).

Third and finally, common sense dictates the same interpretation. Prosecution history estoppel only arises when an amendment has been made that potentially surrenders an

equivalent. *See* Fu, *supra*, at 134 (noting that the more logical time to apply the foreseeability test is at the time of the amendment). The key inquiry is what was known at the time the patentee added the words now being used to estop it from arguing the equivalent.

Amgen strenuously argues that the relevant time period is the time of the application because when amending a patent application, an applicant is limited to the written description and drawings that were in the application at the original filing date and cannot add new matter to an application, even to correct an error in the specification or claims. Amgen's Post-Hr'g Mem. [Document No. 742] at 5. This argument is unavailing because a patentee certainly can—instead of amending—file a continuation-in-part application if the original written description and drawings do not lend themselves to the desired amendment. *See* 35 U.S.C. § 120, 112.[21] In other words, if, as Amgen suggests, there is new matter to add that is necessary to complete or correct the patent description and protect the invention, the patentee can and should re-file the application instead of creating a make-shift amendment to patch up the patent's deficiencies.[22] Therefore, the Court

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[21] A continuation-in-part application generally is one that claims some subject matter common to the parent application but also adds new matter that is not common to and not supported by the parent application. *See e.g.*, *Reynolds Metals Co.* v. *Continental Group Inc.*, 525 F. Supp. 950, 970 (N.D. Ill. 1981); *Chisholm-Ryder Co.* v. *Lewis Mfg. Co.*, 398 F. Supp. 1287, 1289 (W.D. Pa. 1975); *Chemithon Corp.* v. *Procter & Gamble Co.*, 287 F. Supp. 291, 298 (D. Md. 1968). The original filing date, however, applies only to the subject matter that is common to both the parent application and the later-filed application: "[A]ny claims therein that include new matter are only entitled to the actual filing date of the later-filed application, and not the earlier parent application." *Reynolds*, 525 F. Supp. at 970; *Application of Van Langenhoven*, 458 F.2d 132, 136 (C.C.P.A. 1972) ("[S]ubject matter which is first disclosed in a continuation-in-part application is not entitled to the filing date of the parent application."); *Chisholm-Ryder*, 398 F. Supp. at 1289.

[22] Amgen's argument that this is new matter suggests that an amend-

interprets the Supreme Court's holding in *Festo II* as requiring foreseeability to be adjudged relevant to the time the *amendment* was made.

b. *The Federal Circuit's Analysis:* SUPPORTS THIS COURT'S CONCLUSION

Although the Federal Circuit did not explain its conclusion, the recent Federal Circuit opinion in *Festo III* makes clear that foreseeability should be analyzed at the time of the amendment. *Festo III*, 2003 WL 22220526, at *5 (stating repeatedly that this criterion asks "whether the alleged equivalent would have been unforeseeable to one of ordinary skill in the art *at the time of the amendment*") (emphasis added).

C. Has Amgen Rebutted The "Presumption" Of Estoppel?[23]

The following analysis is conducted in light of the Federal Circuit's recent decision in *Festo III*.

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ment was not the correct vehicle to make its desired changes but instead that the more appropriate action would have been for Amgen to have filed a continuation-in-part application. *Cf. Application of Hafner*, 410 F.2d 1403, 1406-07 (C.C.P.A. 1969) (noting that a fatal defect cannot be cured by an amendment). Of course, if it had done this, it would not have had the benefit of the filing date of the earlier application. *Id.*

[23] The Court proceeds directly to determining whether Amgen has rebutted the "presumption" of estoppel. Normally, a court would first analyze whether a *narrowing* amendment had been made for reasons related to patentability (thereby invoking the "presumption" of prosecution history estoppel) and then proceed to determine if the "presumption" was adequately rebutted. *Pioneer Magnetics*, 330 F.3d at 1356-57 (dividing the analysis into three parts: (1) whether the amendment was a narrowing one; (2) whether the amendment was made for reasons related to patentability; and (3) whether the presumption can be overcome); *Soundtube*, 233 F. Supp. 2d at 195-97 (separating the analysis into two parts: "Narrowing Amendment" and "Surrender"). Here, however, the Federal Circuit upheld the Court's determination that the amendment was a narrowing one made to overcome a double patenting objection. Further, the Federal Circuit held that this amendment was therefore related to patentability such that the presumption of prosecution history estoppel would apply. *Amgen II*, 314 F.3d at 1345.

Applying the rules laid out in *Festo II* as interpreted by the Federal Circuit in *Festo III*, the Court begins with the presumption that Amgen has surrendered all the equivalents that fall within the territory between the original claims of the application for the '080 patent and the subsequently narrowed claims of the '080 patent. *See Festo II*, 535 U.S. 733-34; *Festo III*, 2003 WL 22220526, at *4. When the application for the '080 patent was originally filed, it contained 60 claims. These claims did not limit the invention to human EPO nor did they limit the claims to the amino acid sequence of Figure 6. In the third preliminary amendment, Amgen added the following limitation: the "mature human erythropoietin sequence of Figure 6." Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App. [Document No. 708], Tab E at 7.

As explained in *Amgen I*, Figure 6 displays the nucleotide series or DNA sequence of human EPO including both exons (the portions of the sequence that code for the desired protein) and introns (the portions of the sequence that do not code for the protein and are spliced out during transcription). *Amgen I*, 126 F. Supp. 2d at 100. Figure 6 also shows a series of codons, sets of three adjacent nucleotides that determine which of the twenty amino acids are incorporated into a protein at a particular location. *Id.* Each amino acid is identified by its three letter abbreviation representing a codon. *Id.* Figure 6, therefore, demonstrates the deduced amino acid sequence that is arrived at by reading the codons of the DNA encoding the protein. *Id.* Figure 6 numbers the amino acids from -27 to a final position of 166, which is labeled arginine. Because the *original* claims covered all human EPO regardless of the number of amino acids, but the amended claims limited the EPO to Figure 6 (depicting a 166 amino acid sequence), Amgen is presumptively barred from claiming equivalent infringement by a human EPO product containing anything other than that depicted in Figure 6, such as HMR/TKT's EPO which comprises a 165 amino acid sequence.

Amgen attempts to overcome the "presumption" by arguing (1) that HMR 4396, that is, a mature human EPO with a 165 amino acid sequence, was not foreseeable at the time of the application; (2) that the rationale for the amendment bears "no more than a tangential relation to the equivalent in question," *Festo II*, 535 U.S. at 740; and (3) that there is another reason why Amgen could not reasonably be expected to have drafted a claim that encompassed the alleged equivalent.

TKT/HMR argues that Amgen cannot meet the requirements of *Festo II* to rebut the presumption of estoppel because (1) Amgen could have made its claim without specifying the amino acid sequence (Figure 6) in its entirety or at all; and (2) the claims of the original '080 patent covered all EPOs (including the TKT/HMR product) and by amending the claims to include a reference to Figure 6, Amgen surrendered this broad coverage. TKT/HMR's Mem. in Support re: '080 [Document No. 679] at 2.

Before addressing these arguments, a review of the prosecution history is necessary.

1. The Prosecution History Of The '080 Patent

In the first preliminary amendment, the original 60 claims were canceled and new claims 61-67 added. June 6, 1995 Amendment, TKT/HMR's App., Tab E. Of importance to this case are claims 61, 62, 63, and 64.

> 61. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having glycosylation which differs from that of human urinary erythropoietin.
>
> 62. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE.

63. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources and free of other human proteins.

64. The in vivo biologically active erythropoietin product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complementary strands; and

(b) isolating said erythropoietin product therefrom.

Id.

Thereafter, in the Second Preliminary Amendment, Amgen canceled product claims 61-63, amended process claim 64 to specify that it was a non-naturally occurring in vivo biologically active EPO product, and added new "product-by-process" claim 68. *Id*; Amgen's Post-Hr'g Mem. in Support at 12, n.12; December 20, 1995, Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-120.[24]

68. A non-naturally occurring erythropoietin product of the process comprising the steps of:

a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof; and

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[24] It also changed the dependency of claim 65 from "according to claim 61, 62, 63 or 64" to "according to claim 64 or 68." Amgen's Post-Hr'g Mem. at 12; December 20, 1995, Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-20.

b) isolating an erythropoietin product therefrom.

Id.

Amgen then amended the claims again. In this third preliminary amendment, Amgen cancelled claims 64-68 and inserted new claims 69-75. Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E. Claims 69, 70, and 71 became claims 1, 2, and 3 of the '080 patent and are, therefore, the claims of interest here.

> 69. An isolated erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and has glycosylation which differs from that of human urinary erythropoietin.
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> Claim 70. An isolated erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and is not isolated from human urine.
>
> Claim 71. A non-naturally occurring erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6.

Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E at 8.

2. Was The Equivalent Foreseeable?

As discussed *supra*, foreseeability is one of the bases on which to determine whether the standard for rebutting the "presumption" is met. If the equivalent in question was not

foreseeable at the time of the amendment, then the patentee can overcome the "presumption."

Unfortunately for Amgen, it supports its foreseeability argument primarily with expert testimony that addresses knowledge of those skilled in the art *at the time of the application*, as opposed to the time of the amendment (the relevant time period). *Festo II*, 535 U.S. at 741. Amgen claims (and TKT/HMR does not dispute) that it was unknown, at the time of the patent *application*, that the 166th amino acid cleaved off to leave a 165 amino acid sequence. Accordingly, Amgen argues, it was unforeseeable (at the time of the application) that Figure 6's depiction of a sequence of 166 amino acids did not cover all mature human EPOs (including TKT/HMR's HMR 4396). Moreover, it argues that it was unforeseeable that the mature human EPO glycoprotein produced in Example 10 would contain only the 1-165 amino acid sequence.

Crucially, Amgen made admissions in its submissions and oral argument that it—as well as those skilled in the art—knew at the time of the amendment that human urinary EPO had a 165 amino acid sequence. Amgen's Mem. in Support at 10; 7/28/03 Mot. Hr'g Tr. at 71, ll. 11-20; 7/31/03 Mot. Hr'g Tr. at 77, ll. 12-18.[25] In fact, on October 30, 1987, Amgen explained in its FDA product license application that the 166th arginine (depicted in Figure 6) cleaves off leaving 165 amino acids (instead of the originally believed 166):

> The Arg 166, coded for by the erythropoietin gene (Section 2.B) appears to be cleaved post-translationally, resulting in a C-terminus residue of Asp 165. The detailed analysis of the C-terminus of erythropoietin is described later in this Section.

Trial Ex. 2024 at AM 57 007747. Therefore, Amgen cannot meet its burden here. Amgen's argument that this admission

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[25] As discussed, *supra*, consideration of extrinsic evidence is entirely proper under this criterion. *Festo III*, 2003 WL 22220526, at *5-6.

does not show that it was foreseeable that the *amendment (that incorporated the Figure 6 limitation) would be construed* by this Court to exclude human EPO with a 165 amino acid sequence is unavailing at this juncture in the analysis.[26] Simply because the Court's construction (that resulted in a complete surrender of an equivalent human EPO with a 165 amino acid sequence) was not foreseeable at the time of the amendment does not mean that the equivalent was not itself foreseeable—which is the correct inquiry. *See Masco*, 56 Fed. Cl. at 413 (finding unavailing patentee's argument that surrender was not foreseeable because it did not have the Court's claim construction); *SmithKline*, 214 F. Supp. 2d at 592 n.23 ("[T]he issue before this court is whether the patentee had the scientific ability to redraft the claims more broadly . . . .").[27] Although this places a "premium on

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[26] In *Amgen I*, Amgen argued that the amendment should be construed to mean "the fully processed form of the protein secreted by a cell . . . when it transcribes and translates the DNA in Figure 6." *Amgen I*, 126 F. Supp. 2d at 86. TKT/HMR contended that the phrase means "the 166 amino acid sequence of human EPO shown in Fig. 6." *Id.* The Court agreed that the term "mature" meant the fully processed form of EPO secreted by the cell, *id.*, but found that the Figure 6 limitation constricted the meaning of the claim terms to the entire 166 amino acid sequence disclosed in the figure. *Id.* at 100. As will be discussed in greater length, *infra*, Amgen has now submitted extrinsic evidence indicating that Amgen intended the amendment to cover human EPO with a 165 amino acid sequence and that the Patent Office and those skilled in the art interpreted the amendment to do just that. While this evidence is important to the Court's analysis under the third criterion, it is not relevant with respect to whether the equivalent itself was foreseeable.

[27] This is not to say that Amgen's inability to predict the Court's claim construction is wholly irrelevant to whether Amgen can rebut the "presumption." On the contrary, as will be discussed below, there is a reasonableness element to the third criterion of *Festo II*. The fact that Amgen and one skilled in the art would have construed the amendment to cover human EPO with a 165 amino acid sequence may suggest that it is not reasonable to expect Amgen to have drafted the claim otherwise. That being said, this argument is not relevant with respect to whether the

forethought of patent drafting," this premium is not new to the doctrine. *Sage Prods., Inc.* v. *Devon Indus., Inc.*, 126 F. 3d 1420, 1425 (Fed. Cir. 1997); *Johnson & Johnston*, 285 F.3d at 1057 (Rader, J., concurring) ("A foreseeability bar thus places a premium on claim drafting and enhances the notice function of claims. To restate, if one of ordinary skill in the relevant art would reasonably anticipate ways to evade the literal claim language, the patent applicant has an obligation to cast its claims to provide notice of that coverage. In other words, the patentee has an obligation to draft claims that capture all reasonably foreseeable ways to practice the invention."). Here, given its knowledge of human EPO having 165 amino acids, Amgen had "every incentive to redraft the claims as broadly as possible in an effort [to] surrender no more subject matter than necessary to secure the patent." *SmithKline*, 214 F. Supp. 2d at 592. For example, Amgen might have deleted the reference to Figure 6 altogether and claimed "mature human EPO" instead of limiting it to a sequence.[28] Indeed, Amgen admits that it

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equivalent was foreseeable, and, therefore, Amgen cannot rebut the "presumption" based on foreseeability.

[28] TKT/HMR also asserts that Amgen could have drafted a claim that covered human EPO with a 165 amino acid sequence by claiming a fragment or portion of Figure 6 as it did in other claims. TKT/HMR's Mem. in Support at 7. In claim 4 of the '933 patent, "the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof" was claimed. Similarly, the original claim 26 of the 1984 application for the '080 patent sought coverage of "part or all of" the 166 amino acid sequence in Figure 6:

> 26. A synthetic polypeptide having *part or all* of the amino acid sequence set forth in Table VI, other than the residues within the sequence numbered 1 through 20, and having the immunological properties of naturally-occurring human erythropoietin.

Trial Ex. 2411, TKT/HMR's App., Tab C at 64 (emphasis added).

Amgen makes various counter-arguments as to why amendments with these exact words were not possible with respect to the product claims at

"could have sought broader claims that literally encompassed human EPO with a 165 amino acid sequence, and did in fact do so in the '422 patent [U.S. Patent No. 5,955,422]."[29] Therefore, Amgen cannot prevail under this prong of the analysis. The determinative factor here is that the alleged equivalent was foreseeable. In fact, it was known and could easily have been encompassed in the amendment. Thus, Amgen has not met its burden with respect to the foreseeability criterion.

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issue. The Court declines to consider issues that are not determinative here. Amgen does not dispute that it could have claimed "mature human EPO" instead of delineating a sequence. Simply put, if it had merely stated "mature human EPO" instead of specifying Figure 6, arguably it would have served Amgen's purported purpose of distinguishing '080 as "only human" (and not "human and nonhuman") *and* it would have encompassed the alleged equivalent. Any argument that these words would not have been successful in avoiding a double-patenting objection is irrelevant to whether the equivalent was foreseeable and within the patentee's ability to be included in the amendment. *See SmithKline*, 214 F. Supp. 2d at 592 n.23 (noting that "whether the examiner would have accepted the hypothetical amendments" was not relevant to whether the patentee had the scientific ability to draft the claims to encompass the alleged equivalent).

[29] Amgen argues that the relevant inquiry is whether Amgen could have claimed the 1-165 amino acid sequence of Figure 6 specifically—not whether Amgen could have drafted a claim that would have encompassed it. Amgen's Post-Hr'g Mem. at 8-9. The Court disagrees. While it is true that the Supreme Court stated that a patentee could overcome the "presumption" by showing "some other reason suggesting that the patentee could not reasonably be expected to have *described* the insubstantial substitute in question," this must be read in the context of the entire opinion. Elsewhere the Supreme Court used the word "embrace" and "encompass." *Festo II*, 535 U.S. at 734, 741. This is not a judgment about the strength of Amgen's arguments that it could not specifically call out a 165 amino acid sequence because it is new matter. Instead, the Court views these arguments as irrelevant to the analysis because Amgen simply could have employed the more general description noted above, that is, "mature human EPO" or "human erythropoietin."

3. Was The Rationale Underlying The Amendment No More Than Tangentially Related To The Equivalent?

Although the Court has determined that the 1-165 amino acid human EPO equivalent was indeed foreseeable, Amgen can rebut the "presumption" of prosecution history estoppel if it can show by a preponderance of the evidence that the rationale underlying the amendment was only tangentially related to the equivalent. *Festo II*, 535 U.S. at 740.[30] With respect to this standard, more than the others, the *purpose* of the amendment comes to the forefront of the analysis. Contrary to some scholars' views, the correct inquiry is not whether the amendment itself narrows the scope of a claim in

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[30] Neither the Supreme Court, nor the Federal Circuit has yet provided explicit guidance as to what qualifies as a tangential relationship. The few district court cases and the Federal Circuit's *Festo III* decision that address the issue are not particularly helpful here. For example, in *Soundtube* it was clear that the purpose of the amendment was directly related to the equivalent in question because the patentee had "trumpeted the benefits of a constant radius" in its design and "argued that this feature distinguished his invention from the prior art and satisfied section 112 concerns." *Soundtube*, 233 F. Supp. 2d at 198. In *Bosch*, the prosecution history itself showed that the purpose of the amendment was related to the equivalent in question. *Bosch*, 223 F. Supp. 2d at 1172. There, the patentee had argued that the purpose of the amendment was to narrow the location of a certain aspect of the invention, not its shape. *Id.* The Patent Office, however, rejected a final version of the claim that specified the location but not the shape. *Id.* In *Festo III*, one of the amendments was made in response to a rejection and both of the amendments were made to distinguish prior art patents based, partially, on an aspect of the invention relating to the equivalent. *Festo III*, 2003 WL 22220526, at *8- 9. Here, the intrinsic evidence is not so plain. No prior art disclosed any sequence of human EPO let alone one with a 1-165 amino acid sequence. Therefore, no claim can be made that Amgen was trying to distinguish its claims over such equivalent. Moreover, there was no rejection indicating that it was the depiction of 166 amino acids, as opposed communicating "human," that made the difference in patentability.

a way that affects the equivalent in question.[31] If this were the test, it would be an impassable one—the only reason why the dispute arises is *because* the equivalent is related to the amendment and thereby affected. The correct inquiry is whether the *rationale* underlying the amendment, the "reason the amendment was submitted"—not the amendment itself—is more than peripherally related to the equivalent in question. *Festo II*, 535 U.S. at 738, 740 ("Nor is there any call to foreclose claims of equivalence for aspects of the invention that have only a peripheral relation to *the reason the amendment was submitted*. . . .[T]he rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question . . . .") (emphasis added). Thus, the Court must delve deeper to determine whether the rationale underlying the amendment to the '080 patent was tangential to the equivalent in question. While it is undisputed that the amendment was made to avoid a double patenting objection,[32] the parties disagree about why the amendment was so constructed, that is, why Amgen used the exact language it did to distinguish the '080 patent from Amgen's '933 patent. Moreover, in light of the Federal Circuit's mandate that the Court rely only on intrinsic evidence in this criterion, determining the purpose of the amendment is made even more "thorny" because the amendment was not made to address a rejection or objection actually made or described by the Patent Office. *Amgen I*, 126 F. Supp. 2d at 135.

Amgen argues primarily that it amended its claim to specify that the '080 patent referred to the mature *human*

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[31] C. Alan Fu, in his article in the Berkeley Technology Law Journal, noted that the Supreme Court did not specify what the tangential relationship was but that this was the most logical reading of the test. Fu, *supra*, at 136.

[32] To be clear, the '080 claims were never rejected for double patenting; rather, the amendments were made voluntarily and preemptively to distinguish the '080 claims from claim 1 of Amgen's '933 patent. Amgen's Post-Hr'g Mem. at 10; *Amgen I*, 126 F. Supp. 2d at 135.

EPO (which can be described as having the amino acid sequence of Figure 6) and not to distinguish or exclude a 165 amino acid human EPO such as TKT/HMR's HMR 4396. Amgen's Mem. in Opp' n at 12.

The prosecution history supports Amgen's contention. Amgen's '933 patent issued just before this amendment was made. It claimed human and non-human EPO. When the application for the '080 patent was filed, it contained 60 claims, none of which limited the EPO protein products to "human" EPO. Amgen's Post-Hr'g Mem. at 11. As described in detail above, in a preliminary amendment, those original 60 claims were canceled and new claims 61-67 were added. June 6, 1995 Preliminary Amendment, TKT/HMR's App., Tab E. Claims 61-63, product claims, were indeed limited to a human EPO glycoprotein product. *Id.* In a second preliminary amendment, however, all but two claims (which were amended) were cancelled, and a new "product-by-process" claim was added. Amgen's Post-Hr'g Mem. at 12; Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-120. At this point, there is no dispute that the claims, as depicted in the second preliminary amendment were not limited to "human" EPO.[33] In a third preliminary amendment

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[33] Interestingly, two of these claims did indeed mention Figure 6 and one mentioned "human." Process claim 64 limited the technique to "host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6." TKT/HMR's Appendix, Tab E. Process claim 68 recited a technique that involved growing host cells "transformed or transfected with an isolated DNA *sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6* or a fragment thereof." (emphasis added). Amgen's Post-Hr'g Mem. at 12; Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-120. TKT/HMR does not assert that these two claims limit the claim to *human EPO* and Amgen argues that it does not so limit it. This may be because these are process, not product, claims. Regardless, because it is undisputed, the Court does not read the emphasized phrases so to limit the claims.

(the amendment at issue in this case), Amgen changed the product-by-process claims back to product claims adding the limitation at issue here: "the mature erythropoietin amino acid sequence of Figure 6." Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E (canceling claims 64-68 and adding new claims 69-75).

TKT/HMR's main counter-argument is that Amgen had previously referred to an "isolated *human* erythropoietin glycoprotein" and, therefore, could not have been amending in order to distinguish this claim on the basis of human EPO versus non-human EPO. TKT/HMR's Mem., Tab E (emphasis added). TKT/HMR, however, compares the third (and final) preliminary amendment with the first preliminary amendment, failing to account for the fact that the second preliminary amendment did not so limit the claims to human EPO. Neither Amgen nor TKT/HMR provide any evidence as to why Amgen changed the claims from product claims to product-by-process claims and then back again, nor do they provide evidence as to why the claims were (in the first amendment) limited to human EPO and then not so limited (in the second amendment) and then finally limited again (in the third amendment). *See, e.g.*, 7/31/2003 Mot. Hr'g Tr. at 76, ll. 1-25 (describing the chronology of amendments and stating that Amgen does not know why the limitation to "human" was dropped out when the claim was put into a product-by-process claim). Regardless of the reason why Amgen switched back and forth, the chronology and language of the amendments support Amgen's position that it added the amendment in question (the third amendment) to distinguish the '080 patent from the '933 patent on the basis that '080 was limited to *human* EPO.[34]

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[34] Both parties agree that a patentee can patent a product for human *and* non-human EPO and also patent a product for only human EPO. This does not run awry of the double-patenting rule because the same invention is not claimed in both patents. An EPO product could literally infringe the

This position is also supported by Amgen's statements to the Patent Office. In its remarks accompanying the third preliminary amendment, Amgen told the Patent Office that it distinguished the '080 patent from the '933 patent by "specifying that the claimed subject matter [of the '080 claims] comprises the mature *human* erythropoietin sequence of Figure 6." Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E at 9 (emphasis added).[35]

In further support of Amgen's argument that it did not amend to distinguish the '080 patent from human urinary EPO that has a 165 amino acid sequence, it points to the fact that it told the Patent Office that glycosylation and source limitations—not the Figure 6 limitation—distinguished the EPO of its amended '080 claims from human urinary EPO. *Id.*[36] This indicated to the Patent Office that Amgen was not

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claims of one patent without literally infringing the claims of the other. For example, monkey EPO could literally infringe the patent that claims both human and non-human EPO, but it would not literally infringe the patent that claims only human EPO. *See In re Vogel*, 422 F.2d 438, 441 (C.C.P.A. 1970) (noting that 35 U.S.C. § 101 "prevents two patents from issuing on the same invention. . . . By 'same invention,' we mean identical subject matter. Thus, the invention defined by a claim reciting 'halogen' is not the same as that defined by a claim reciting 'chlorine,' because the former is broader than the latter.").

[35] Interestingly, Amgen did not include the word "human" in the actual third preliminary amendment. Amgen claims it did not do so because it was "superfluous" with the portion of the amendment that referred to the sequence of Figure 6. Amgen's Reply Mem. [Doc. No. 733] at 8. In other words, Figure 6—which contains 166 amino acids—sufficiently signified human EPO (as opposed to non-human). This, however, is extrinsic evidence to which the Court cannot resort in analyzing this criterion.

[36] The exact remarks are:

> Applicant notes that [the amended '080 claims] all differ in scope from glycoprotein claim 1 of [the '933 patent] in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6. [Claim 1 of the '080], (like glycoprotein claim 1 [of the '933 patent]), recites carbohydrate differences in compari-

differentiating its product from prior art based on the Figure 6 limitation but instead based on glycosylation and source limitations. This comports with the state of the art at the time. There was no prior art disclosing a 1-165 sequence for human EPO and thus Amgen had no need to distinguish its claims over any such equivalent. To the extent that it needed to distinguish prior-art human urinary EPO, Amgen did so by including the limitations noted above regarding differences in glycosylation and isolation from human urine.

Further, Amgen points out that at the time this amendment was made, Amgen had already disclosed to the Patent Office the reference that reveals that human EPO is missing the COOH-terminal Arg 166 amino acid residue. Amgen's Post-Hr'g Mem. at 11; Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 140 (disclosing to the Patent Office that the 166 arginine cleaved off by referencing Recny).[37] Given that Amgen and the Patent Office knew that human EPO (and, therefore, example 10 of the '080 patent) actually had a 1-165 amino acid sequence, a "reasonable inference" is that the amendment was not made to surrender human EPO with a 1-165 amino acid sequence or distinguish 1-166 from 1-165 because that would have illogically resulted in either Amgen surrendering its preferred embodiment or pursuing a patent that it and the Patent Office knew to be incorrect. *Festo II*, 535 U.S. at 724 (noting that the purpose of applying estoppel

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> son to human urinary [EPO] and claim [2] recites a negative limitation with respect to isolation from human urine.

Id.

[37] Recny refers to the article that reveals that the urinary hormone is missing the COOH-terminal Arg 166 amino acid residue. Recny, et al., *Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin*, J. Biol. Chem., 262(35), 17156-63 (Dec. 15, 1987). This reference is cited in the '080 patent disclosure as one that was reviewed by the Examiner. Amgen's Post-Hr'g Mem. at 11; Trial Ex. 3 ('080 Patent), TKT/HMR's App., Tab A.

is "to hold the inventor to the representations made during the application process and the inferences that may *reasonably* be drawn from the amendment") (emphasis added).[38] To infer such a chain of events would not be reasonable.

TKT/HMR counters, in essence, with the argument that all of this history is irrelevant. It contends that *any* amendment made to avoid double patenting *cannot* be tangential "because it goes to the heart of the reasons why the claims were ultimately allowed." TKT/HMR's Post-Hr'g Mem. at 35. This argument fails, however, because it conflates the inquiry regarding whether the amendment was made for patentability reasons, that is, whether the presumption of prosecution history estoppel applies in the first place, with the inquiry into the rationale for the amendment at hand. The rationale cannot be more than tangentially related to the equivalent in question—but it can be more than tangentially related to patentability issues—if this were not so, this tangentiality standard would be circular and insurmountable because prosecution history estoppel applies when a narrowing amendment is made for patentability reasons. If HMR/TKT's interpretation were correct, arguably the Supreme Court would not have

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[38] This reasonable inference—that the amendment was not made to differentiate a 165 amino acid EPO from a 166 amino acid EPO—would not *alone* be sufficient to overcome the presumption. Although one scholar deems the tangential standard met when the patentee proves there is no objective intent to disclaim, *see* J. Jason Lang, *The German Resolution: A Proposed Doctrine of Equivalents Analysis and a Flexible Rule of Prosecution History Estoppel For Biotechnology*, 52 Emory L.J. 427, 478 (2003), upon close reading of *Festo II*, it appears such proof is not enough. The prosecution history must affirmatively show that the purpose of the amendment was no more than tangentially related to the equivalent in question—not just a lack of intent to surrender territory. Here, however, proof of lack of intent to surrender is not the only proof supporting Amgen's contentions. As discussed earlier, the prosecution history also affirmatively supports that the purpose of the amendment was unrelated to the equivalent in question.

held that tangentiality was one way of overcoming the "presumption;" and the Federal Circuit, which agreed with this Court that the amendment was made for patentability reasons, *Amgen II*, 314 F.3d at 1345, would likely have noted on remand that, of the potential ways to rebut the "presumption," tangentiality was foreclosed.

In sum, Amgen has shown by a fair preponderance of the evidence that the amendment at issue was made for a reason only tangentially related to the equivalent in question. Therefore, the Court holds that Amgen has satisfied the "tangential" criterion as defined by the Federal Circuit in *Festo III*.[39]

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[39] As suggested earlier, the Court reaches this conclusion because the Federal Circuit's *Festo III* decision directs the Court to conduct its analysis based only on intrinsic evidence. Had the Federal Circuit interpreted the Supreme Court's decision to allow for resort to extrinsic evidence—as this Court so interpreted the decision—Amgen would not have prevailed with respect to this criterion. Two pieces of extrinsic evidence—ironically submitted by Amgen itself—demonstrate that the amendment was indeed more than tangentially related to the equivalent in question.

1) *Admissions by Amgen's Counsel*

Amgen's counsel stated repeatedly at the July 28, 2003 motion hearing that the purpose of the amendment was not only to limit the EPO claimed in '080 to human (as opposed to human and non-human) but to specify a sequence. "[W]e wanted claims that limited the invention to the sequence so that it specified the sequence of the protein." 7/28/2003 Mot. Hr'g Tr. at 72, ll. 24-25. "The amendment was made *to distinguish claims that had no sequence* and embraced EPOs of multiple species *to claim a protein that has the human sequence*." *Id.* at 73, ll. 14-16 (emphasis added). Although it is likely that Amgen wanted to specify a sequence to avoid potential objections related to the strict enablement and written description requirements of patent law, *see* Lang, *supra*, at 464 (stating that "[t]he strict enablement and written description requirements often limit claiming of biotechnological inventions to specific DNA and amino acid sequences"), such a rationale does not negate Amgen's admissions. Notwithstanding any ulterior motive for submitting the amendment, by stating that it wanted specifically to claim a sequence, Amgen admits that at least part of the amendment's rationale was more than tangentially related to

any human amino-acid sequence including a 1-165 amino acid sequence, the equivalent in question.

An analogy is appropriate here. Suppose a patentee described, in an amendment, a four-cornered object in detail that *happened* to depict a square. The patentee may be able to prove that the rationale for the amendment was not related to the shape of the object and, therefore, was not related to an equivalent that specifically claimed a rectangular shape. An assertion by the patentee to the Court, however, that it made the amendment to specify a particular shape suggests that the amendment indeed would be more than tangentially related to the equivalent that depicted a rectangle. *Cf. Bosch*, 223 F. Supp. 2d at 1171 (noting that "a strong argument can be made that the reason JSB used the phrase 'in a semicircle' was to convey that the lever goes around the internal gear, not to convey that the lever must be of a particular shape"). The same logic holds true here, especially when considered in conjunction with another submission by Amgen that is discussed below.

2) *Expert Testimony Regarding Interpretation of the Amendment and Amgen's Intentions*

Amgen asserts and supports with expert testimony that Amgen intended and those skilled in the art interpreted its amendment to cover human urinary EPO with a 165 amino acid sequence. Amgen plainly stated that it "intended the sequence limitation to cover human EPO compositions having the 1-165 amino acid sequence." Amgen's Post-Hr'g Mem. at 2; *see also* Amgen's Mem. in Support at 6-10. While a patentee's subjective intent ought not be considered by the Court when unsupported by the prosecution history, *Vitronics*, 90 F.3d at 1584, this intent is supported by the file wrapper. Amgen disclosed to the Patent Office the reference that reveals that human EPO—Example 10 of the '080 patent—has 165 amino acids; and Amgen explained to the Patent Office that other limitations in the '080 claims—not the Figure 6 limitation—distinguished its claimed EPO from all other human urinary EPO. Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E at 9. These two pieces of prosecution history support Amgen's assertion that it wrote the amendment *in order to cover* the recently discovered human EPO with a 165 amino acid sequence and that the Patent Office believed that this amendment so covered it. If the Patent Office did not believe this, it arguably would not have allowed the amendment for it would have made the patent specification incorrect because the patent specification included Example 10, then understood to result in an EPO with a 165 amino acid sequence.

4. Some Other Reason?

As discussed above, the Federal Circuit stated that the third criterion should be a narrow one and that courts should consider only the prosecution history record "[w]hen at all possible" in conducting its analysis. *Festo III*, 2003 WL 22220526, at *6. That being said, the Court did not detail an exhaustive list of the type of circumstances that satisfy the criterion or decide when resort to extrinsic evidence would be deemed necessary. Nor did it describe "what evidence outside the prosecution history record, if any, should be considered in determining if a patentee has met its burden under this third rebuttal criterion." *Festo III*, 2003 WL 22220526, at *6. Therefore, the boundaries of analysis under this criterion will be refined by courts, such as this one, faithfully interpreting *Festo II*, *Festo III*, and any future relevant decisions by the Supreme Court and the Federal Circuit.

In further support, an expert (and also the author of the amendment) testified that the claim "would cover . . . 166, 165, whatever the process format is in the particular [host] cell." Borun Trial Test., Amgen's App., Tab D at 2884-85. This testimony supports Amgen's contention regarding its intent and that those skilled in the art would have interpreted the amendment to cover human EPO with a 165 amino acid sequence.

While all of the intrinsic evidence shows by a fair preponderance that the purpose of the amendment was *not* to *differentiate* human EPO with 166 amino acids from human EPO with 165 amino acids (as discussed earlier), when considered in combination with the extrinsic evidence, it shows at least part of the rationale underlying the amendment was to depict a sequence that covered the recently discovered human urinary EPO with 165 amino acids. As such, the rationale would be more than tangentially related to the equivalent in question. Although the amendment may have been specifically designed to avoid double patenting by claiming human EPO, it was also specifically designed to cover human urinary EPO, which was then known by Amgen, the Patent Office and those skilled in the art to have the 1-165 amino acid sequence. Thus, when considering the intrinsic *and* extrinsic evidence, it is apparent that the amendment is more than peripherally related to the "insubstantial substitute," human urinary EPO with 165 amino acids.

While resort to extrinsic evidence will not always be necessary to determine if this third criterion has been met, objectively determining whether "some other reason" reasonably prevented the patentee from describing the alleged equivalent in its narrowed claim, may—like the foreseeability analysis—"depend on underlying factual issues relating to . . . the state of the art and the understanding of a hypothetical person of ordinary skill in the art at the time of the amendment." *Id.* at *5. This is so even if the "other reason" is the shortcomings of language—the one reason the Federal Circuit suggested would meet this criterion—because, without a thorough understanding of the state of the technology and how certain language would be interpreted by one skilled in the art at the time of the amendment, the Court would not be able to determine if adequate language existed that should have been used by the patentee.

While it is true that courts regularly—and in fact ought—construe claims without resort to expert testimony regarding how one skilled in the art would interpret the claims, a court's claim construction often narrows the claim in a way that may have been unintended by the patentee. Such narrowing is the reason why the doctrine of equivalents was created—to capture, despite the inadequacies of language, the essence of the invention in light of technological advances. *See generally Festo II*, 535 U.S. at 731-32; *Graver Tank*, 339 U.S. at 607; *Autorigo Co.*, 384 F.2d at 397. Undeniably, there is a difference between how a court approaches claim construction and how it approaches the doctrine of equivalents and prosecution history estoppel. The policy of avoiding all extrinsic evidence except when necessary in claim construction is to ensure that a court is determining solely the literal terms of the claim, that is, those claims of which the public was notified. The policy behind the doctrine of equivalents, on the other hand, is more equitable in nature; it seeks to determine what the patentee was surrendering and any "reasonable inferences" that can be drawn from the patentee's

representations. *Festo II*, 535 U.S. at 737-39; see also *Festo III*, 2003 WL 22220526, at *4 ("Prosecution history estoppel has traditionally been viewed as equitable in nature, its application being 'guided by equitable and public policy principles.'") (citations omitted). Thus, reasonableness, although not a part of claim construction, is central to the doctrine of equivalents.

The idea of reasonableness was reinforced by the Supreme Court in *Festo II*. It held, generally, that to rebut the presumption of surrender "the patentee must show that at the time of the amendment one skilled in the art could not *reasonably be expected* to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo II*, 535 U.S. at 741 (emphasis added). Moreover, the Supreme Court also specifically included an analysis of reasonable expectations of the patentee in the third criterion to rebut the presumption. *Id.* Thus, the Court's analysis at this stage—as opposed to that during claim construction—includes a reasonableness inquiry that involves questions of equity, even after *Festo II*.

The reasonableness inquiry as defined by *Festo II*, however, is now different than it used to be. Before *Festo II*, the reach of prosecution history estoppel was decided by considering what a competitor or one skilled in the art reasonably would have determined was surrendered by the amendment. *Modine Mfg. Co.* v. *U.S. Intn'l Trade Comm'n*, 75 F.3d 1545, 1555 (Fed. Cir. 1994); *Zenith Labs.* v. *Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1424 (Fed. Cir. 1994); *Hoganas AB* v. *Dresser Indus., Inc.*, 9 F.3d 948, 952 & n.15 (Fed. Cir. 1993); *Haynes Intn'l, Inc.* v. *Jessup Steel Co.*, 8 F.3d 1573, 1578 & n.4 (Fed. Cir. 1993). After *Festo II*, however, the focus is not on what those skilled in the art reasonably would have concluded was relinquished but on what subject matter the patentee itself reasonably should have included in the amendment. *Leading Cases*, *supra*, at 409 ("The Court's new

test shifts the estoppel inquiry from the ex post perspective of a reasonable competitor to the ex ante perspective of the person drafting the patent."); Golian, *supra*, at 599. Under the pre-*Festo II* approach, a patentee could expect to retain all but those equivalents surrendered in the amendment. Now, the patentee is on notice that all equivalents that reasonably could be expected to be included are surrendered. In other words, a patentee survives prosecution history estoppel if it can show that drafting the claim to include the equivalent was not a reasonable expectation. Thus, even after *Festo II*, when analyzing the third criterion, the Court must make a reasonableness inquiry, but now it must ask what a reasonable patentee *could be expected* to have done. *See, e.g.*, Fu, *supra*, at 137 (noting that *Festo II* includes a reasonableness test, that is, an equitable consideration). This reasonableness inquiry requires the Court to look into the circumstances and in some cases, like the one at hand, to consider extrinsic evidence.

Amgen's main argument under this third rebuttal criterion is that it could not reasonably be expected to have described the equivalent in question because competitors and those skilled in the art would have interpreted the amendment, at the time it was made, actually to cover the equivalent. In support, Amgen submits extrinsic evidence in the form of expert testimony, suggesting that the drafter of the amendment in question—and those skilled in the art—interpreted the amendment to cover all human EPO whether it had 165 amino acids or 166. Borun Trial Test., Amgen's App., Tab D at 2885.[40]

There is also intrinsic evidence supporting this position. As explained earlier, the prosecution history shows that the

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[40] The drafter is one skilled in the art. The fact that he interpreted the amendment in this way supports the contention that others skilled in the art would have interpreted the amendment similarly.

Patent Office Examiner was informed by Amgen that human urinary EPO, such as that produced by the preferred embodiment depicted in Example 10, has the 1-165 amino acid sequence of Figure 6. Recny, *supra*, Trial Ex. 53 at 17156; Amgen's Post-Hr'g Mem. in Support at 11. In other words, the Patent Office examiner had the information that human urinary EPO has the exact amino acid sequence shown in Figure 6, except for the 166th arginine. Moreover, the reference that discloses how the 166th arginine is cleaved off was revealed to the Patent Office during the prosecution and cited as a reference in the '080 patent disclosure. Trial Ex. 3 ('080 Patent), TKT/HMR's App., Tab A at 8; Amgen's Post-Hr'g Mem. in Support at 11 n.26. Thus, given Example 10, either the Patent Office was knowingly enabling the prosecution of an incorrect patent, or it too interpreted the amendment to cover human urinary EPO with a 1-165 amino acid sequence.[41]

Overall then, the evidence supports the contention that Amgen, the Patent Office, and, importantly, those skilled in the art interpreted the claims as amended literally to encompass the particular equivalent in question here, an EPO with a 165 amino acid sequence.

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[41] Without Example 10, the fact that Amgen was claiming human EPO with 166 amino acids would not itself have been incorrect because, at the time of the amendment, it was not known that *no* human EPO comprising 166 amino acids existed. According to counsel, at that time there were "reports in the literature that there are expressed by certain cells 166 forms of EPO and there are expressed by other cells 165." 7/31/03 Mot. Hr'g Tr. at 77, ll. 23-25, and 78, l. 1. In other words "what was known was the gene sequence for human EPO encoded 166 amino acids" and "when that gene sequence is put in certain cells it gets 165. For example, when it was put in the CHO cells in Example 10 of Lin's patent it produced 165." *Id.* at 78, ll. 11-16. To this day, it is actually unknown whether there is a human EPO with 166 amino acids. *Id.* at ll. 3-4. "EPO has never been purified from human blood. It is so vanishingly small, no one has ever gotten to its actual human form." *Id.* at ll. 6-8.

While the correct inquiry, after *Festo II*, is not what those skilled in the art or a reasonable competitor would conclude was surrendered by the amendment, a competitor's reasonable interpretation of the amendment is necessarily relevant in determining what the patentee reasonably can be expected to have drafted.[42] Claims are drafted for a particular audience—those skilled in the art. Given that there is evidence that those skilled in the art would have interpreted the amendment to include human EPO with a 165 amino acid sequence—the equivalent in question—it would not be reasonable to expect Amgen to have drafted the claim differently. While the Court did indeed construe the claim differently,[43] such construction should not prevent the Court from resorting to this extrinsic evidence—evidence it did not consider during claim construction[44]—to understand what can be reasonably expected of the patentee. While such extrinsic evidence may be inappropriate in claim construction, as discussed earlier, it

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[42] In *Haynes*, the Federal Circuit recognized that the vantage point of one skilled in the art is consistent with the vantage point of a reasonable competitor. *Haynes*, 8 F.3d at 1578 n.4.

[43] As mentioned, *supra*, in *Amgen I*, Amgen argued that the amendment should be construed to mean "the fully processed form of the protein secreted by a cell . . . when it transcribes and translates the DNA in Figure 6." *Amgen I*, 126 F. Supp. 2d at 86. TKT/HMR contended that the phrase means "the 166 amino acid sequence of human EPO shown in Fig. 6." *Id.* The Court agreed that the term "mature" meant the fully processed form of EPO secreted by the cell, *id.*, but found that the Figure 6 limitation limited the meaning of the claim terms to the entire 166 amino acid sequence disclosed in the figure. *Id.* at 100.

[44] The record indicates that the Court did not rely on extrinsic evidence to construe the claim. *Amgen I*, 126 F. Supp. 2d at 86, n.12 (noting that the Court did not receive evidence during the *Markman* hearing); *see also, Amgen I*, 126 F. Supp. 2d at 81 (commenting on the importance of separating claim construction from issues of infringement to avoid conflating fact and law and noting that during the *Markman* hearing the Court considered counsel's arguments relating to the specification and prosecution history but that "evidence was neither offered nor admitted").

appropriately is considered in the context of this criterion's reasonableness inquiry.

It is this part of the criterion, the reasonableness element, that TKT/HMR completely ignores and that is determinative here. TKT/HMR focuses its counter-argument on what Amgen, the patentee, *could have* drafted. TKT/HMR argues, as it did under the foreseeability prong, that Amgen could have easily drafted a claim that literally encompassed the equivalent. While the Court finds this assertion to be true, as discussed *supra*, Amgen has shown by a fair preponderance of the evidence that those skilled in the art (and the Patent Office) interpreted the amendment to encompass the equivalent.[45] The fact that the Court later determined—under a pre-*Festo II* analytic framework—that this amendment did not encompass all theoretically possible human EPO does not justify holding Amgen to the literal terms of the amended claim. The Supreme Court made clear that *Festo II* does not go that far and that, if it did, it would defeat the purpose of the doctrine of equivalents:

> The amendment does not show that the inventor suddenly had more foresight in drafting of claims than the inventor whose application was granted without amendments having been submitted. It shows only that he was familiar with the broader text and with the difference between the two. As a result there is no more reason for holding the patentee to the literal terms of an amended claim than there is for abolishing the doctrine of equivalents altogether and holding the patentee to the literal terms of the patent.

Festo II, 535 U.S. at 738. Here, the evidence shows that Amgen was familiar with the broader text, human *and* non-

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[45] Importantly, TKT/HMR has not produced any evidence that those skilled in the art interpret the claim differently. In fact, all of the evidence supports Amgen's contentions. Thus, under the preponderance of the evidence hurtle, Amgen has met its burden.

human. It amended its claims to specify human EPO and believed that its patent and this amendment encompassed the alleged equivalent. It is not reasonable to expect one skilled in the art to have used different claim language when the language that was used was interpreted by those skilled in the art to be sufficiently descriptive.[46] This is just the sort of "shortcoming[] of language" or "linguistic" limitation to which the Federal Circuit referred in its opinion. *Festo III*, 2003 WL 22220526, at *6, *8. Here, the amendment made clear that the patent did not cover nonhuman but failed (according to the Court's claim construction) to make clear that it covered human EPO with a 165 amino acid sequence. While this drafting error was fatal to Amgen's literal infringement argument, it is not fatal to Amgen's ability to rebut the "presumption" under this prong of the analysis. As the Supreme Court explained, "language is an imperfect fit for invention," the "narrowing amendment may demonstrate what the claim is not; but it may still fail to capture precisely what the claim is." *Festo II*, 535 U.S. at 739; Lang, *supra*, at 478-86 (commenting that language limitations or an art's unpredictability should work to overcome the presumption.) A patentee should not be able to attain through litigation that

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[46] Furthermore, it is clear from the record that claiming any amino acid sequence 165 or 166 is like claiming a moving target. No one knows what is really expressed in humans because, as Amgen's counsel explained, "EPO has never been purified from human blood. It is so vanishingly small, no one has ever gotten to its actual human form." 7/31/03 Mot. Hr'g Tr. at 78, ll. 6-8. To that end, biotechnology is itself an "unpredictable technology." Lang, *supra*, at 457. This unpredictability impairs a patentee's ability to draft claims to cover the full scope of the patent because the art "generally offer[s] only a handful of linguistic tools for circumscribing an invention." *Id.* at 477, 485 ("The unpredictability of this art alone should rebut the presumption of prosecution history estoppel."); Borun Trial Test., Amgen's App., Tab D at 2884-85 (explaining that after it became known that the 166th amino acid was chopped off, the Genetic Institute and others challenged the conclusion that a CHO cell product terminates with the 165th amino acid).

which was surrendered during the prosecution history. Here, however, Amgen has shown by a fair preponderance of the evidence that, while the amendment failed to capture precisely what the claim is, the 165 amino acid equivalent was not surrendered.

Although this analysis is not directly contrary to the holdings of *Festo III*, the Federal Circuit strongly indicated that it will—when the issue is ripe before it—cabin in the third criterion with respect to the use of extrinsic evidence and the circumstances that satisfy the criterion. Thus, this Court rests its decision on the tangential criterion but holds in the alternative that Amgen has also met the third criterion, that is, Amgen has shown by a fair preponderance of the evidence that some other reason exists that suggests that at the time of the amendment it could not *reasonably* be expected to have drafted the claim to describe the insubstantial substitute in question.

III. CONCLUSION

In light of the Federal Circuit's narrow interpretation of the third criterion and admonition to rely only on intrinsic evidence whenever possible, the Court's analysis under the "some other reason" category and its resort to extrinsic evidence is less certain. Ironically, however, the "tangential" criterion—originally rejected on the basis of extrinsic evidence—is now persuasive once the focus narrows to the prosecution history alone. Frankly, a holding based on the "tangential" criterion seems less satisfactory and more artificial than the Court's original holding based on "some other reason," yet I deem it compelled by the Federal Circuit's less than generous reading of the Supreme Court's decision in *Festo II*. Perhaps the disjunction I perceive arises from the incredibly complex nature of recombinant DNA technology compared to the mechanical technology present in the *Festo* line of cases. Future decisions will doubtless refine

these matters. In any event, either way Amgen "wins," that is, rebuts the presumption of prosecution history estoppel.

Accordingly, upon further consideration in light of *Festo III*, HMR/TKT's motion for judgment that Amgen is estopped from asserting equivalent infringement of the '080 patent [Doc. No. 678] is DENIED and Amgen's motion for judgment that claims 2-4 of the '080 are infringed under the Doctrine of Equivalents [Doc. No. 659] is ALLOWED.

SO ORDERED.

/s/ William G. Young
WILLIAM G. YOUNG
CHIEF JUDGE

Supreme Court, U.S.
FILED
MAR 22 2007
OFFICE OF THE CLERK

No. 06-1291

In the Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI APPENDIX VOLUME II OF II

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APPENDIX D

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

01-1191, -1218

AMGEN INC.,
Plaintiff-Cross Appellant,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals, Inc.)
and TRANSKARYOTIC THERAPIES, INC.,
Defendants-Appellants.

DECIDED: January 6, 2003

Before MICHEL, CLEVENGER, and SCHALL, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* MICHEL. Dissenting opinion [p. 410a, *infra*] filed by *Circuit Judge* CLEVENGER.

MICHEL, *Circuit Judge.*

Plaintiff-Cross Appellant Amgen Inc. ("Amgen") is the owner of numerous patents directed to the production of erythropoietin ("EPO"), a naturally occurring hormone that controls the formation of red blood cells in bone marrow. Amgen markets and sells EPOGEN®, a highly successful commercial embodiment of the patented erythropoietin. Seeking to impede defendants-appellants Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (collectively "TKT") from commercializing a competitive EPO product, Amgen filed a declaratory judgment action in the United States District Court for the District of Massachusetts in April

1997, alleging that TKT's Investigational New Drug Application ("INDA") infringed United States Patent Nos. 5,547,933 ("the '933 patent"); 5,618,698 ("the '698 patent"); and 5,621,080 ("the '080 patent"). The complaint was amended in October 1999 to include United States Patent Nos. 5,756,349 ("the '349 patent") and 5,955,422 ("the '422 patent"), which issued after suit was filed.

After a three-day *Markman* hearing, the case was tried to the court for 23 days over the course of four months. In January 2001, the district court issued an exhaustive 244-page opinion in which it: (i) construed the disputed claims; (ii) held each of the patents enforceable; (iii) held the '080, '349 (product claims), and '422 patents valid and infringed; (iv) held the '698 patent not infringed; and (v) held the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. *Amgen, Inc. v. Hoescht Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 57 USPQ2d 1449 (D. Mass. 2001). On appeal, TKT urges reversal on the grounds that the patents in suit are all unenforceable, that the district court's claim construction was erroneous, and alternatively, if that claim construction was correct, that the court's validity determinations were erroneous. Amgen asserts, in its cross appeal, that the district court committed error: (i) by comparing the accused process to the examples in the specification rather than the limitations of the method claims of the '349 and '698 patents; and (ii) by holding the '933 patent invalid for failure to comply with § 112. We heard oral argument on May 7, 2002.

We commend the district court for its thorough, careful, and precise work on what is indubitably a legally difficult and technologically complex case. There is no doubt that the court marshaled tremendous time and resources in its effort to reach correct results. Nevertheless, because we must conclude that the court committed certain errors of law in certain of its validity and infringement determinations, we cannot affirm the judgment in its entirety.

We affirm *in toto* the district court's claim construction. We also affirm: (i) its determination that none of the patents in suit is unenforceable for inequitable conduct; (ii) its contingent determination that the '933 patent is invalid under § 112 ¶ 1; (iii) its grant of summary judgment of infringement of '422 patent claim 1; (iv) its determination that the '080, '933, '349, and '698 patents are not anticipated by the Sugimoto reference; and (v) its determination that '349 patent claims 1, 3-4, and 6 are infringed. Because the district court misapplied the law, however, we vacate: (i) its determination that the '933 patent is not infringed; (ii) its determination that the '080 patent is infringed under the doctrine of equivalents; (iii) its determination that the '080, '349, and '422 patents are not invalid; and (iv) its determination that the asserted method claims of the '698 patent and '349 patent claim 7 are not infringed. Accordingly, we remand for the district court to reconsider: (i) whether the '080, '349, and '422 patents are obvious in light of the Sugimoto prior art or anticipated or obvious in light of the Goldwasser prior art; (ii) whether the '422 patent is anticipated by Sugimoto reference (and whether Amgen can prove its nonenablement); (iii) whether the asserted claims of the '698 patent and '349 patent claim 7 are infringed by the accused method; and (iii) whether the '080 patent is infringed under the doctrine of equivalents. In sum, as further explained in detail below, we affirm in part, vacate in part, and remand for further proceedings consistent herewith.

BACKGROUND

As the district court set out in painstaking detail the basics of the underlying technology, we will provide only a brief summary here. The reader's familiarity with the fundamentals of molecular biology, genetics, and recombinant DNA technology necessary to this appeal is presumed.[1]

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[1] For further reading on these subjects, *see generally* Robert A.

EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow. Red blood cells are critical because they contain hemoglobin, a protein responsible for transporting oxygen from the lungs to peripheral tissues. Because EPO is produced in the kidney, patients with chronic kidney (renal) failure lack normal levels of EPO and, as a result, have a sub-optimal number of red blood cells—a condition called anemia. The therapeutic goal for treating anemic patients is to increase the "hematocrit level," which represents the ratio of red blood cells to total blood volume, to normal or near-normal levels. This is accomplished through the introduction of additional EPO into the patient's system.

The implementation of this seemingly simple solution, introduction of exogenous EPO, proved to be difficult. Because human EPO is produced in very small amounts (even from the healthy human kidney), it is difficult to obtain by conventional methods. Early attempts to recover EPO from plasma or from human urine ("urinary EPO" or "uEPO") were unsuccessful because such recovery employed techniques that were complicated, yet still resulted in a low-yield, high-impurity, or unstable EPO end product. '933 patent, col. 6, line 60-col. 7, line 42. Similar attempts using antibody techniques failed because of difficulty in providing for the large-scale isolation of quantities of EPO from mammalian sources sufficient for further analysis, clinical testing, or therapeutic use. *Id.*, col. 9, lines 2-8. The first successful method of production of a therapeutically effective amount of erythropoietin used recombinant EPO ("rEPO") techniques; Amgen is recognized as the pioneer. *See, e.g.*, *Molecular Biology and Biotechnology* at 108.

Meyers, ed., *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers (1995); Benjamin Lewin, *Genes VII*, Oxford Univ. Press (2000); James D. Watson et al., *Recombinant DNA* (2d ed. 1992).

Amgen scientist Dr. Fu-Kuen Lin is the named inventor on all five patents in suit. Instead of attempting to purify EPO from natural sources, Lin isolated and characterized monkey and human EPO genes, then used conventional recombinant DNA technology to produce large amounts of rEPO. '933 patent, col. 13, lines 50-53. Lin was able to determine the entire DNA sequence of human EPO and from that, its predicted amino acid sequence. *Id.*, Fig. 6; col. 10, lines 65-col. 11, line 2. Using the isolated human EPO gene, Lin described several methods for producing therapeutically effective amounts of human EPO using an expression vector.[2] *Id.*, col. 21, line 42-col. 25, line 27.

EPOGEN®, the commercial embodiment of Amgen's patented EPO product, is produced by the method disclosed in patent specification Example 10. That example describes the production of human EPO through transfection (introduction) of exogenous DNA into host Chinese hamster ovary ("CHO") cells. The CHO host cell, using its own transcription machinery, then expresses human rEPO in abundance, which then accumulates in the host cell cytoplasm or in the culture media. *Id.*, col. 37, lines 43-49. The rEPO so recovered has the same or similar amino acid sequences and biological properties as naturally occurring human EPO, but differs in its "glycosylation," *i.e.*, in the patterns of branched carbohydrate chains that attach to the protein. '933 patent, col. 10, lines 34-41.

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[2] An "expression vector" is a circular piece of DNA (or "plasmid") that is inserted into a host cell to produce (or "express") a protein. The expression vector carries the gene encoding for the protein of interest (in this case human EPO), a marker that assures that the vector is properly introduced into the host cell, and a promoter site that the host will recognize to transcribe the vector's DNA. *See generally* Thomas E. Crieghton, ed., *Encyclopedia of Molecular Biology*, vol. 2, John Wiley & Sons, Inc. (1999) at 883-86.

The patents in suit, which all claim priority to a December 1983 application long since abandoned, are continuations of a common ancestor—United States Patent No. 4,703,008—which was at issue in this court's landmark decision in *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).[3] The '933 patent issued on August 20, 1996, containing 14 claims drawn primarily to a non-naturally occurring EPO product with certain characteristics. At issue in this lawsuit are claims 1, 2, and 9 (with the disputed claim terms here and below underscored):

> 1. A *non-naturally occurring erythropoietin glycoprotein* product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having *glycosylation which differs from that of human urinary erythropoietin.*
>
> 2. The *non-naturally occurring EPO glycoprotein* product according to claim 1 wherein said product has a higher molecular weight than *human urinary EPO* as measured by SDS-PAGE.
>
> 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

The '698 patent issued on April 8, 1997, containing nine claims drawn to a process for producing a glycosylated erythropoietin polypeptide. At issue are claims 4-9:

> 4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase

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[3] Because the patents in suit share an identical disclosure, all citations will be to the '933 specification unless otherwise noted.

production of reticulocytes and red blood cells comprising the steps:

a) growing, under suitable nutrient conditions, *vertebrate cells* comprising promoter DNA, other than human erythropoietin promoter DNA, *operatively linked to DNA* encoding *the mature erythropoietin amino acid sequence of* FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, *vertebrate cells* comprising amplified *DNA encoding the mature erythropoietin amino acid sequence of FIG. 6*; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

7. The process of claim 6 wherein *said vertebrate cells* further comprise amplified marker gene DNA.

8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

9. The process according to claims 2, 4 and 6 wherein said cells are *mammalian cells.*

The '080 patent, which issued with seven claims on April 15, 1997, claims both an isolated erythropoietin glycoprotein and

a method for therapeutically administering a pharmaceutical composition thereof. Only product claims 2-4 are at issue:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6* and is not isolated from human urine.
>
> 3. A *non-naturally occurring erythropoietin glycoprotein* having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6.*
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.

The '349 patent, which issued on May 26, 1998, contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

> 1. *Vertebrate cells* which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising *non-human DNA sequences that control transcription of DNA encoding human erythropoietin.*
>
> 3. *Vertebrate cells* according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 4. *Vertebrate cells* which can be propagated in vitro which comprise *transcription control DNA sequences*,

other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay

6. *Vertebrate cells* according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, *vertebrate cells* according to claim 1, 2, 3, 4, 5, or 6.

Last, the '422 patent, containing two claims directed to therapeutically effective pharmaceutical compositions of EPO, was granted on September 21, 1999. Only claim 1 is in dispute:

1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is *purified from mammalian cells grown in culture.*

The district court conducted the *Markman* hearing in late March and early April 2000 in advance of Amgen's motion for summary judgment of infringement. The court entertained oral argument, aided by demonstrative exhibits, but heard no witness testimony and received no evidence. *Amgen*, 126 F. Supp. 2d at 81, 57 USPQ2d at 1455. At the close of the hearing, the court announced its claim constructions from the bench; these oral rulings were included and expounded upon in the written opinion ruling on the merits following trial. *Id.* at 84-94, 57 USPQ2d at 1457-64.

Immediately following the *Markman* hearing, the court turned to Amgen's pending motion for summary judgment of

infringement of '422 patent claim 1 and '349 patent claims 1, 3-4, and 6. As to the '422 patent, the district court found: (1) that it was uncontradicted that the accused product, HMR4396, was a pharmaceutical composition; (2) that it necessarily contained a therapeutically effective amount of human erythropoietin (otherwise, the filing of an INDA would be pointless); and (3) that the record evidence demonstrated that HMR4396 contained a pharmaceutically acceptable diluent, adjuvant, or carrier as claimed in claim 1. *Id.* at 94-95, 57 USPQ2d at 1455-56. The sole remaining question was whether the accused erythropoietin product had been "purified from mammalian cells grown in culture." The court found, in light of its claim construction that the term "mammalian" comprises human cells, that the last limitation had been met. *Id.* at 95-96, 57 USPQ2d at 1466. The court therefore granted summary judgment of infringement of '422 patent claim 1.

Trial commenced on May 15, 2000. When Amgen rested at the close of its infringement case, the court granted TKT's motions for judgment of non-infringement of the '698 patent and literal non-infringement of the '080 patent. *Id.* at 99-104, 57 USPQ2d at 1469-73. At the close of TKT's rebuttal case, the court granted Amgen's motion for judgment of validity, finding that TKT had not carried its burden of clearly and convincingly proving anticipation or obviousness. *Id.* at 104-17, 57 USPQ2d at 1473-82. The remaining issues were taken under advisement. The court's opinion issued on January 19, 2001, and these timely cross-appeals followed. Vested with jurisdiction under 28 U.S.C. § 1295(a)(1), we address below the myriad issues before us.

DISCUSSION

I

The rules are by now well known. Because claim language defines claim scope, the first step in an infringement analysis

is to construe the claims, *i.e.*, to determine the scope and meaning of that which is allegedly infringed. *Markman v. Westview Instr., Inc.*, 52 F.3d 967, 976, 34 USPQ2d 1321, 1326 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 38 USPQ2d 1461 (1996). To properly construe the claims, a court must examine the claims, the rest of the specification, and, if in evidence, the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576-77 (Fed. Cir. 1996). Thereafter, the properly construed claims are compared to the accused product or process to determine whether each of the claim limitations is met, either literally or equivalently. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1365, 62 USPQ2d 1658, 1662 (Fed. Cir. 2002).

There are two general areas of dispute TKT raises regarding the district court's claim construction. First, TKT urges that the court erred by failing to limit the asserted claims to exogenous DNA, despite the fact that none of the claims in suit contain an "exogenous DNA" limitation. Second, TKT asserts that the court erred by refusing to limit the terms "vertebrate," "mammalian," and "non-naturally occurring"—each of which appear in varying degrees within the asserted claims—such that they exclude host human cells which, of course, are used by the accused infringers. We consider the trial court's claim construction—a matter of law—afresh on appellate review. See *Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1455, 46 USPQ2d 1169, 1173 (Fed. Cir. 1998) (en banc).

A

We turn first to address a threshold definitional dispute that carries with it important consequences for the infringement issues decided by the district court and facing us on appeal, to wit, what is the distinction between exogenous, as opposed to endogenous, DNA in recombinant DNA parlance? According to TKT, it practices an innovative process using homologous

recombination: it takes the ordinarily unexpressed endogenous (or "native") EPO gene in human cells and transfects "a viral promoter and certain other DNA" that does not encode EPO. That "other" DNA is inserted into the chromosome at a pre-determined, targeted location upstream from the endogenous EPO gene to produce what TKT has termed "Gene-Activated EPO," or "GA-EPO." TKT contrasts this method with that of Amgen, which TKT asserts undeniably uses exogenous DNA.

None of the asserted claims contain either an "exogenous DNA" or "endogenous DNA" limitation.[4] Based upon representations allegedly made by Amgen during the prosecution of the patents in suit, however, TKT argues that many of the claims the district court construed should have been defined narrowly to include only exogenous DNA. The district court rejected this argument, as do we.

"It is the claims that measure the invention." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121, 227 USPQ 577, 585 (Fed. Cir. 1985) (*en banc*). Because the claims are best understood in light of the specification of which they are a part, however, courts must take extreme care when ascertaining the proper scope of the claims, lest they simultaneously import into the claims limitations that were unintended by the patentee. *See, e.g., Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 950, 28 USPQ2d 1936, 1938 (Fed. Cir. 1993) ("It is improper for a court to add extraneous limitations to a claim, that is limitations added wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim." (citation omitted)).

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[4] That is not to say that there are no claims that have such a limitation. Unasserted claim 3 of the '933 patent, for example, does contain such a limitation: "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." col. 38, lines 26-29.

The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim. "If we once begin to include elements not mentioned in the claim in order to limit such claim . . ., we should never know where to stop." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 990, 50 USPQ2d 1607, 1610 (Fed. Cir. 1999) (quoting *McCarty v. Lehigh Val. R.R.*, 160 U.S. 110, 116 (1895)).

Amgen's inventive EPO product, according to the disclosure in the '933 patent, is "uniquely characterized by being the product of prokaryotic or eucaryotic host expression (e.g., by bacteria, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." '933 patent, col. 10, lines 15-20. In discussing United States Patent No. 4,237,224 (issued to Cohen), the '933 patent defines "exogenous DNA" by reference as DNA that is foreign to the host organism. *See id.* col. 2, lines 41-47 ("[T]he Cohen et al. patent first involve[s] manufacture of a transformation vector by enzymatically cleaving viral or circular plasmid DNA to form linear DNA strands. Selected foreign ('exogenous' or 'heterologous') DNA strands usually including sequences coding for desired product are prepared in linear form through use of similar enzymes."). During the prosecution of Serial No. 08/468,369, which became the '349 patent, the examiner commented that the application "teaches and enables only cells that have been transformed with exogenous DNA that encodes erythropoietin (EPO) that have the high EPO production required by the claims." TKT asserts, as a result, that its GA-EPO product and process fall outside the scope of the asserted claims because Amgen repeatedly has characterized its claimed products and processes as requiring the use of exogenous EPO DNA, and hence the claims should be limited thereto.

Guided by our principles of claim construction, we agree with the district court that TKT improperly seeks to import

the "exogenous" limitation into the claims. The plain meaning of the claims controls here, and they plainly are not so limited. The statement that the invention is "uniquely characterized" by the expression of exogenous DNA sequences does not impel us to accept TKT's position when the asserted claims do not contain such an express limitation. In fact, TKT's position is undermined by the doctrine of claim differentiation, as reference to other claims clearly indicates that Amgen did not intend to limit the invention to the use of exogenous DNA. Unasserted claim 3 of the '933 patent, for example, is virtually identical to claim 1, save for the express limitation regarding the use of "exogenous DNA" (underlined portioned indicating differences).

Claim 1	Claim 3
A non-naturally occurring *erythropoietin* glycoprotein product *having* the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.	A non-naturally occurring glycoprotein product *of the expression in a mammalian host cells of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing* the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of huma urinary erythropoietin.

Our court has made clear that when a patent claim "does not contain a certain limitation and another claim does, that limitation cannot be read into the former claim in determining either validity or infringement." *SRI Int'l*, 775 F.2d at 1122, 227 USPQ at 586; *see also O.I. Corp. v. Tekmar Co., Inc.*, 115 F.3d 1576, 1582, 42 USPQ2d 1777, 1781 (Fed. Cir.

1997) (expressing the notion that there are practical limits to the doctrine of claim differentiation: "the doctrine cannot alter a definition that is otherwise clear from the claim language, description, and prosecution history."). There is a rebuttable presumption that different claims are of different scope. *See Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1366-67, 53 USPQ2d 1814, 1817 (Fed. Cir. 2000); *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1479-80, 45 USPQ2d 1429, 1434 (Fed. Cir. 1998).

The examiner's statement in the prosecution history gives us no pause, as the basis for his rejection was not because transformation with exogenous DNA was not taught, but because "the high EPO production required by the claims" was not. *See* J.A. at 1302 ("The instant application does not guide one of ordinary skill in the art in the discovery of non-transformed vertebrate cells that are capable of the high EPO production recited in the instant claims, [as demonstrated in the reference,] each of which discloses levels of EPO production by vertebrate cells in culture that are far below those levels required in the instant claims."). TKT's position is further undermined because the asserted claims issued. We must presume the examiner did his job, and if he truly thought that the specification taught or enabled only the use of exogenous DNA, the asserted claims would not have issued.

In the end, TKT has not directed our attention to anything in the intrinsic record that rebuts the presumption that the plain meaning of the terms controls. Accordingly, we conclude that the scope of the asserted claims should not be limited to the expression of exogenous DNA.

B

TKT asserts, in addition to the exogenous/endogenous distinction discussed above, that the district court misconstrued the terms "non-naturally occurring," "vertebrate cells,"

and "mammalian cells"—which appear in many of the asserted claims—to include human cells. Reviving the same argument the district court rejected below, TKT contends Amgen expressly disavowed the use of human cells to make human EPO.

The district court found that the definition of the term "non-naturally occurring" can be discerned through the doctrine of claim differentiation. Specifically, the court concluded that TKT's proffered construction must fail in light of '933 patent claim 3, discussed previously, which claims a "*non-naturally occurring* glycoprotein product of the expression in a *mammalian* host cell of an exogenous DNA sequence encoding *human* erythropoietin . . . ." By its terms, then, this claim would cover the expression of human DNA in a cat host cell, for example, because a cat is a mammal. The court thus concluded that the phrase "non-naturally occurring" would be redundant in claim 3 if the phrase had the meaning TKT sought to ascribe to it. Further, because the patent specification compares the biological activity of synthetic products to "EPO isolates from natural sources" or "natural EPO isolates," the court concluded that non-naturally occurring simply means "not occurring in nature." *Amgen*, 126 F. Supp. 2d at 90-91, 57 USPQ2d at 1462-63.

Similarly, finding that the term vertebrate is widely known and understood to cover anything with "a segmented bony or cartilaginous spinal cord [which obviously includes humans]," *id.* at 85, 57 USPQ2d at 1457-58, the court adopted Amgen's proposed construction. The court also adopted Amgen's proposed construction of the term "mammalian cells" appearing in '422 patent claim 1 and '698 patent claim 9 under a similar rationale. *Id.* at 84-86, 57 USPQ2d at 1458.

We indulge a heavy presumption that a claim term carries its ordinary and customary meaning. *CCS Fitness*, 288 F.3d at 1366, 62 USPQ2d at 1662; *see also Gart v. Logitech, Inc.*,

254 F.3d 1334, 1341, 59 USPQ2d 1290, 1295 (Fed. Cir. 2001). Although TKT is correct that the prosecution history is always relevant to claim construction, it is also true that the prosecution history may not be used to infer the intentional narrowing of a claim absent the applicant's clear disavowal of claim coverage, such as an amendment to overcome a rejection. *See York Prods., Inc. v. Central Tractor & Farm Fam. Ctr.*, 99 F.3d 1568, 1575, 40 USPQ2d 1619, 1624 (Fed. Cir. 1996). No such clear disavowal occurred here.

We agree with Amgen that the specification expressly describes humans as a subset of mammals, and mammals, in turn, as a subset of vertebrates. *See* '933 patent, col. 4, lines 47-48; col. 10, line 21. Moreover, the specification can fairly be read to, if not expressly, disclose the use of human DNA in human host cells in culture:

> Conspicuously comprehended are expression systems involving vectors of homogeneous origins applied to a variety of bacterial, yeast, and mammalian cells in culture as well as to expression systems not involving vectors . . . . *In this regard, it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of 'exogenous' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host.*

'933 patent, col. 37, lines 33-43 (emphasis added). The astute reader will observe what appears to be a breakdown in the parallelism of the sentence emphasized in the block quote above. Specifically, the reference to the expression of "monkey origin DNA in monkey host cells in culture and human host cells in culture" seems a bit nonsensical because the expression of monkey origin DNA in human host cells is perforce the expression of exogenous DNA. The original 1983 application from which all the patents in suit claim

priority, by contrast, contained language that upholds the parallelism of the sentence and logically makes sense. It read, in pertinent part: "[I]t will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and *human DNA in* human host cells in culture constitute instances of 'exogenous' DNA expression." J.A. at 2862 (emphasis added).

TKT boldly asserts that the variance between the original application and the patents in suit bespeaks some volitional act by Amgen to narrow the scope of the asserted claims in light of certain experimental data. In particular, TKT advances a theory whereby Amgen intentionally removed the language from subsequent applications (allegedly) because test results using human cells were not good, and later admitted (during an opposition proceeding against the European counterpart patent) that the omission was not inadvertent. But the record contains a more benign explanation as to what happened. According to the testimony of Dr. Lin, he was unaware of, and therefore did not authorize, the change. Further, the prosecuting attorney testified in his deposition that to the best of his knowledge the error was a typographical error.

But even assuming that the error was intentional, the district court's claim construction would not be foreclosed: our precedent is clear that claims are not perforce limited to the embodiments disclosed in the specification. *E.g.*, *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344, 60 USPQ2d 1851, 1856 (Fed. Cir. 2001) ("[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."). Here, the patent plainly discloses the use of human host cells in culture, and our review of the record indicates no "clear disavowal" sufficient to undercut the express disclosure in the specification.

As a result, we are satisfied that the terms "non-naturally occurring," "vertebrate," and "mammalian" should be construed as they were by the district court, in a manner consistent with their plain meaning. Accordingly, we reject TKT's attempt to limit the scope of the asserted claims under an unduly constricted reading of the specification.

C

The final claim construction issue TKT raises is aimed at the district court's alleged failure to discern "source and process" limitations in claims of the '080, '349, and '422 patents. According to TKT, the trial court erred by concluding that the asserted claims are product claims, i.e., that they are directed to a structural entity that is not defined or limited by how it is made. TKT summarily states that this holding must be erroneous because, it asserts, the patentability of the claims depended on the process since "Amgen tried, but failed, to distinguish rEPO from prior art EPOs based on physical differences." We do not agree.

It is telling that neither in the briefing nor at oral argument did TKT direct us to any specific statement in the prosecution history to support the contention that the patentability of the product claims in suit depended upon the process by which those products are obtained. In fact, the original claims of at least one of the patents (the '080 patent) were drafted as product-by-process claims, which claims were cancelled and replaced with "pure" product claims. This is strong evidence that both the patentee and the examiner viewed the claims that ultimately issued as lacking a process component. *See Vanguard Prods., Inc. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372, 57 USPQ2d 1087, 1089 (Fed. Cir. 2000) ("Parker Hannifin argues that the prosecution history shows that the Vanguard inventors viewed co-extrusion as 'fundamental' to manufacture of the claimed gasket, thereby imposing this process of manufacture upon the product claims . . . . However, review of the prosecution history shows that during

examination the examiner as well as the applicant treated the product claims as directed to the product itself, and examined the application accordingly.").

In any event, we are not convinced that the source limitations in the asserted claims convert the claims into anything other than product claims. As to the '080 patent, the "non-naturally occurring" limitation in claims 3 and 4 merely prevents Amgen from claiming the human EPO produced in the natural course. By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use *negative* limitations such as "non-human" and "non-natural" to avoid rejection under § 101. See *Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 923, 18 USPQ2d 1677, 1680 (Fed. Cir. 1991). The district court arrived at a similar conclusion, *Amgen*, 126 F. Supp. 2d at 89, 57 USPQ2d at 1462-63, and TKT has not demonstrated any error in that conclusion. Similarly, the "not isolated from human urine" limitation in claims 2 and 4 of the '080 patent simply requires that the claimed EPO, however made, be obtained from a source other than human urine. Each of these limitations only excludes human EPO from specific sources and does not restrict the claimed EPO to that produced from any particular source or by any particular method. In sum, claims 2, 3, and 4 of the '080 patent remain broadly drawn to the described "erythropoietin glycoprotein" or "pharmaceutical composition" produced by any method, or obtained from any source, other than those specifically excluded.

As to the '422 patent, the limitation "purified from mammalian cells grown in culture" in claim 1 clearly limits the source of the EPO used in the claimed "pharmaceutical composition." The limitation only speaks to the source of the EPO and does not limit the process by which the EPO is expressed. Rather, the claim is broadly drawn to a "pharma-

ceutical composition" having certain elements, one of those being EPO "purified from mammalian cells in culture." This reading is in line with the district court's construction and, again, TKT directs us to no error.[5]

II

It is axiomatic that claims are construed the same way for both invalidity and infringement. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 842 F.2d 1275, 1279, 6 USPQ2d 1277, 1280 (Fed. Cir. 1988). But because the features of the accused product or process are often undisputed, this axiom invites a common approach in the appellate arguments by accused infringers: the principal argument challenges the correctness of a trial court's broad claim construction; the contingent argument, assuming the trial court's claim construction is affirmed, challenges validity under 35 U.S.C. § 112 ¶ 1 of the asserted patents in light of that broad construction. *See, e.g., Adv. Cardiovascular Sys. v. Medtronic, Inc.*, 265 F.3d 1294, 60 USPQ2d 1161 (Fed. Cir. 2001); *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 37 USPQ2d 1618 (Fed. Cir. 1996); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983). TKT employs that approach here. We therefore think it appropriate to address the relevant § 112 issues before turning to the issue of infringement.

Section 112 of the patent statute describes what must be contained in the patent specification. Among other things, it must contain "a written description of the invention, and of the manner and process of making and using it . . . [such] as to enable any person of ordinary skill in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112 ¶ 1. Thus, this statutory language mandates satisfaction of two separate and independent requirements: an applicant

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[5] We do not hold that these limitations lack meaning, only that they mean just what they say. Accordingly, they limit only the source from which the EPO is obtained, not the method by which it is produced.

must both describe the claimed invention adequately and enable its reproduction and use. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Third, though not in issue here, he must disclose what he considers the best mode of practicing his invention.

A

The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Id.* at 1561, 19 USPQ2d at 1115 (citation omitted). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem v. Gen-Probe, Inc.*, 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted). Because of its fact intensive nature, we review a district court's decision on the adequacy of written description for clear error. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (citations omitted).

In addressing TKT's written description arguments, the district court carefully examined whether Amgen's specification adequately described the full breadth of the claims. In the end, the district court rejected TKT's written description challenge, finding that TKT had proven its case only by a preponderance of the evidence—*not* the clear and convincing standard required as a matter of law. Acknowledging the

presence of "a genuine dispute between the expert witnesses," the court weighed the testimony and found that the evidence showed that the descriptions adequately described to those of ordinary skill in the art in 1984 the use of the broad class of available mammalian and vertebrate cells to produce the claimed high levels of human EPO in culture. *Amgen*, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507. In so doing, the court credited in particular the testimony of Amgen's expert, Dr. Harvey Lodish, who testified, among other things, that there might be "minor differences" in applying the method of the disclosed examples (utilizing CHO and COS-1 (monkey) cells) to any vertebrate or mammalian cells, but that those of ordinary skill could "easily" figure out those differences in methodology. *Id.*, 57 USPQ2d at 1507.

Much of TKT's argument on appeal challenging this finding dovetails with its claim construction arguments we have already found lacking. For example, TKT asserts that the Amgen patents do not satisfy the written description requirement because: (1) Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells; (2) Amgen deleted use of exogenous human EPO DNA in human cells from its applications;[6] (3) Amgen expressly excluded the use of endogenous EPO DNA; (4) Amgen emphasized that the advantage of its invention was "freedom from association with human proteins"; and (5) in using the "uniquely characterized" language to describe the polypeptides of the invention, Amgen identified exogenous EPO DNA as an essential element of the invention. As a result of these shortcomings, argues TKT, it has clearly and convincingly proven invalidity under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473,

[6] We addressed this point in our claim construction analysis on pages 17-18 *ante*, finding that the written description did not exclude human cells from the scope of the claims. That analysis suffices here as well.

45 USPQ2d 1498 (Fed. Cir. 1998), and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). We are not persuaded that these precedents mandate reversal of the trial court's factual findings as clearly erroneous regarding the written descriptions.

First, in addressing the adequacy of the written description of the '422 patent and with respect to TKT's exogenous DNA arguments, the district court noted:

> When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise after the patent application is filed. *See United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251 [9 USPQ2d 1461, 1465] (Fed. Cir. 1989); *In re Koller*, 613 F.2d 819, 824-25 [204 USPQ 702, 707] (Fed. Cir. 1980); *see also In re Hogan*, 559 F.2d 595, 606 [194 USPQ 527, 538] (C.C.P.A. 1977). Instead, section 112 only requires the Court to determine whether the specification conveys to one of ordinary skill in the art as of 1984 that Dr. Lin invented the subject matter claimed in the patents-in-suit. *Reiffin*, 214 F.3d at 1346 [*Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1346, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000)]. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim—not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made.

Amgen, 126 F. Supp. 2d at 150, 57 USPQ2d at 1508; *see also id.* at 152, 57 USPQ2d at 1509 (discussing the '080 patent), 154 n.51, 57 USPQ2d at 1510 (discussing the '349 patent). The district court therefore considered TKT's exogenous

DNA arguments and, for the reasons stated above, rejected them. On appeal TKT has not argued that its legal analysis was erroneous. Because we have not been directed to any case law to the contrary, we conclude the district court's legal conclusion based on *Phillips Petroleum* was not erroneous and that it properly handled the exogenous DNA issue.

We move now to TKT's argument that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention. We held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself—not merely a recitation of its function or a reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. *See Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613. Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.[7] Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell—not the human DNA itself. This difference alone sufficiently distinguishes *Eli Lilly*, because

[7] Indeed, Amgen's patents appear to satisfy the sequence requirement in *Eli Lilly* insofar as Figure 6 of the patents expressly discloses the complete (albeit slightly incorrect) sequence of human genomic EPO DNA and the encoded DNA.

when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." *Eli Lilly*, 119 F.3d at 1567, 1568, 43 USPQ2d at 1406.[8] Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders *Eli Lilly* listless in this case. *Amgen*, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507.

TKT's remaining arguments rely on *Gentry Gallery*. However, we see *Gentry Gallery* as similarly inapt. TKT would have us view *Gentry* as a watershed case, in reliance on an isolated statement—probably only dicta—that one of ordinary skill in the art would clearly understand that the location of the reclining controls on the claimed sectional sofa "was not only important, but essential to [the] invention." 134 F.3d at 1480, 45 USPQ2d at 1503. But as we recently indicated in *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1323, 62 USPQ2d 1846, 1850-51 (Fed. Cir. 2002), "we did not announce [in *Gentry*] a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." *See also Vas-Cath,* 935 F.2d at 1565, 19 USPQ2d at 1114; *cf. Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 345 (1961) ("[T]here is no legally recognizable or protected

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[8] There is no issue here as to *in haec verba* description because, as stated in the body of the opinion, in contrast to "cDNA"—that clearly does not describe the actual sequence of the cDNA—the words "mammalian cells" and "vertebrate cells" convey exactly what they are. Thus, this aspect of the holding in *Eli Lilly* is also inapplicable here.

'essential element,' 'gist' or 'heart' of the invention in a combination patent."). Understood in this light, one sees the holding in *Gentry* for what it really was: an application of the settled principle that a broadly drafted claim must be fully supported by the written description and drawings. *See Cooper Cameron*, 291 F.3d at 1323, 62 USPQ2d at 1850-51. After considering extensive testimony from both parties, the district court held this principle met and TKT failed to demonstrate that this analysis was clearly erroneous factually or based on an error of law. *Amgen*, 126 F. Supp. 2d at 149-50, 57 USPQ2d at 1507-08.

To the extent the particular facts of *Gentry* are relevant, we also find it distinguishable. First, there is a fundamental difference between Amgen's patented invention and the invention in *Gentry*. In *Gentry* the invention *was* the placement of reclining controls on a central console on a unit of a sectional sofa so as to allow the sofa to have two independent reclining seats face in the same direction (solving a problem present in the prior art). 134 F.3d at 1475, 45 USPQ2d at 1499. The undisclosed element leading to the *Gentry* court's holding of invalidity for lack of an adequate description was a location for the controls other than on the console—leading to a different and undescribed *product. See id.* at 1479, 45 USPQ2d at 1502-03. Amgen's invention is not the location of the control sequences and EPO DNA in relation to the cell, but rather the production of human EPO using those sequences. Thus, the undisclosed element TKT urges invalidates Amgen's product claims is a different *method* (endogenous activation) of making the claimed compositions. But, as the district court noted, under our precedent the patentee need only describe the invention as claimed, and need not describe an unclaimed method of making the claimed product. *Amgen*, 126 F. Supp. 2d at 150, 57 USPQ2d at 1507 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824-25, 204 USPQ at 707); *see also Vas-Cath*, 935 F.2d at 1563-64, 19 USPQ2d at 1117.

This factual difference alone is sufficient to distinguish this case from *Gentry*.

Second, the statements by the patentee in the written description in this case fall short of what *Gentry* prohibits. The court in *Gentry* concluded that the inventor had clearly expressed in the written description that he considered his invention to be limited to the specific location of the controls on the console on the sofa ("the only possible location") and that any variation was "outside the stated purpose of the invention." *Gentry Gallery*, 134 F.3d at 1479, 45 USPQ2d at 1503. Indeed, in *Gentry* the inventor testified that he only considered locating the controls outside of the console—and only broadened his application claims accordingly—after seeing Gentry's competitors introduce products with controls located off the console. *Id.* Here, to be sure, Amgen made statements that its invention is "uniquely characterized" by exogenous expression of DNA. '933 patent col. 10, lines 15-20. When considered in context, however, these statements do not lead to the same conclusion as in *Gentry*. Amgen's statements simply do not clearly indicate that exogenous expression is the *only* possible mode of the invention or that other methods were outside the stated purpose of the invention. Instead, Amgen begins the background section of its written description by stating "[t]he present invention relates generally to the manipulation of genetic materials and, more particularly, to recombinant procedures making possible the production of polypeptides possessing part or all of the primary structural conformation and/or one or more of the biological properties of naturally occurring erythropoietin." '933 Patent, col. 1, lines 18-23. Because of this lack of clear statements by the patentee limiting the claimed invention (and in light of the case law discussed, *ante*), we cannot invalidate a patent for failure to describe a method of producing the claimed compositions that is not itself claimed. Nor could the patentee have described the other method, as it was not developed until 10 years later. We see *Gentry Gallery* as in-

applicable in this regard. In light of the evidentiary record and TKT's inability to persuade us that precedent requires a contrary result, we hold that the district court's finding that Amgen satisfied the written description requirement is not clearly erroneous.

B

The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Before the district court, TKT bore the burden of clearly and convincingly proving facts showing that the claims were not enabled. *E.g.*, *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1375, 52 USPQ2d 1129, 1141 (Fed. Cir. 1999). Enablement is a question of law; we therefore review the trial court's determination *de novo*, deferring to its assessment of subsidiary facts underlying the legal question unless clearly erroneous. *Bruning v. Hirose*, 161 F.3d 681, 686, 48 USPQ2d 1934, 1939 (Fed. Cir. 1998).

TKT contends that the asserted claims are invalid for lack of enablement. Taking a position that virtually mirrors the written description (and claim construction) arguments previously rejected, TKT posits that the specifications do not enable an ordinarily skilled artisan to practice the full scope of the asserted claims without undue experimentation because they fail to describe the production of EPO using human cells or endogenous human EPO DNA. At bottom, TKT complains

that the court erred by failing to follow its findings to their logical conclusion.[9]

But the district court made thorough and complete factual findings supporting its holding that the claims were not proven not enabled, expressly incorporating many of its factual determinations made with respect to written description. As to TKT's endogenous/exogenous arguments, the court concluded the arguments were inapplicable as a matter of law for two reasons. First, "where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed." *Amgen*, 126 F. Supp. 2d at 160, 57 USPQ2d at 1515 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824-25, 204 USPQ at 707; *In re Hogan*, 559 F.2d at 606, 194 USPQ at 538); *see also id.* at 161, 57 USPQ2d at 1516 (discussing the '080 patent), 163-64, 57 USPQ2d at 1518 (discussing the '349 patent). Thus, the specification's failure to disclose the later-developed endogenous activation technology cannot invalidate the patent. *Id.* at 160, 57 USPQ2d at 1516. Second, "the law makes clear that the specification need teach only one mode of making and using a claimed composition." *Id.* at 160, 57 USPQ2d at 1515 (citing Johns *Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998); *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)); *see also Durel Corp.*

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[9] TKT refers here to the district court's statement that "it appears that Dr. Lin claimed far more than he delivered." *Amgen*, 126 F. Supp. 2d at 158, 57 USPQ2d at 1514. Although this statement does seem out of kilter with the court's ultimate holding, we understand it in light of how close the court viewed the issue: "After much reflection, the court finds that Amgen survives [the enablement challenge], albeit barely." *Id.* at 157, 57 USPQ2d at 1513.

v. Osram Sylvania Inc., 256 F.3d 1298, 1308, 59 USPQ2d 1238, 1244 (Fed. Cir. 2001). This conclusion again makes the specification's failure to disclose TKT's endogenous activation technology legally irrelevant. *Amgen*, 126 F. Supp. 2d at 160, 57 USPQ2d at 1515. We reach the same conclusion on appeal, as TKT has not persuaded us that the district court's conclusions in this regard were erroneous.

Focusing specifically on the '422 patent, the enablement inquiry is whether Amgen has enabled all pharmaceutical compositions comprising "a therapeutically effective amount of human erythropoietin," "a pharmaceutically acceptable diluent, adjuvant or carrier," and human erythropoietin "purified from mammalian cells grown in culture." The court found that the specification described and enabled various possible diluents and carriers and provided specific information on effective dosages and therapeutic effect in mice. *Id.* at 148, 57 USPQ2d at 1506. Amgen also described and enabled at least one way of obtaining EPO purified from mammalian cells in culture: the genetic manipulation of CHO and COS-1 cells, followed by both described and other well known purification techniques. Finally, the court accepted testimony indicating that an ordinarily skilled artisan would infer from the COS-1 (monkey) and CHO cell examples that similar outcomes could be expected from other mammalian cells since all mammalian cells produce and secrete hormones like EPO by means of the same fundamental processes. *Id.* at 159, 57 USPQ2d at 1514-15. These are all findings of fact and they have not been shown to be clearly erroneous.

As to the '080 patent, the inquiry is whether Amgen has enabled the production of all EPO glycoproteins having "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells," "the mature erythropoietin amino acid sequence of FIG. 6," and "[are] not isolated from human urine" or "non-naturally occurring." The court noted that Amgen disclosed the *in vivo*

biological effect of EPO upon hematocrit levels in mice and adequately disclosed the sequence of the amino acid residues in figure 6. *Id.* at 151, 57 USPQ2d at 1508-09. Amgen also described and enabled at least one method of producing EPO that was both "non-naturally occurring" and "not isolated from human urine": the genetic manipulation of CHO and COS-1 cells. The court noted with particularity that even TKT's witness, Dr. Kingston, agreed that if one of ordinary skill in the art followed the teachings of Example 10, then such a person could successfully practice the claimed invention. *Id.* at 161, 57 USPQ2d at 1516.

We address the product claims of the '349 patent in more detail, as they differ slightly from the patents we discussed above. The '349 patent claims genetically manipulated "vertebrate cells"—a composition—having certain characteristics and properties, including an ability to produce the claimed levels of human EPO.[10] The enablement question thus posed is this: having disclosed one way to make the claimed EPO-producing cell, is Amgen entitled to claim all such cells that "can be propagated *in vitro*," comprise "non-human DNA sequences that control transcription," transcribe "DNA encoding human erythropoietin," and produce the claimed amount of EPO? While our precedent does hold that disclosure of one or two species *may* not enable a broad genus, *e.g.*, *In re Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45, the district court made several fact-findings indicating that any gaps between the disclosures and the claim

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[10] Following the dissent's "machine" analogy, the "machine" is a genetically altered vertebrate cell containing transcription control sequences used to transcribe a human EPO gene to express the claimed levels of human EPO. Simply altering the way the human EPO gene is inserted or activated—whether it be through transformation with exogenous DNA or through activation of an endogenous gene—does not make this a different "machine" once built; rather, it only changes the way it was "constructed."

breadth could be easily bridged. *See, e.g.*, *Amgen*, 126 F. Supp. 2d at 149, 57 USPQ2d at 1514 (crediting Amgen's expert Dr. Lodish's statement that "one of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that were used in this example, that other vertebrate cells, mammalian cells, could have been used"); *cf. Enzo Biochem*, 188 F.3d at 1367-68, 1372, 52 USPQ2d at 1133, 1136-37 (affirming nonenablement of claims to anti-sense DNA technology applied to all eukaryotic and prokaryotic organisms because anti-sense was a "highly unpredictable technology" and a "high quantity of experimentation" would be needed to practice the invention outside of the disclosed example); *Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45 (holding the examiner did not err in rejecting as nonenabled claims drawn to all genetically-engineered cyanobacteria expressing a given protein because the claimed 150 genera of cyanobacteria represent a vast, diverse, and poorly understood group; heterologous gene expression in cyanobacteria was "unpredictable"; and the patent's disclosure referred to only a genus). The district court found that a skilled artisan could readily have used various cultured vertebrate and mammalian cells to produce human EPO, and this fact was buttressed by numerous post-filing publications that demonstrated the extent of the enabling disclosure. *Amgen*, 126 F. Supp. 2d at 162, 57 USPQ2d at 1517 (citing *Gould v. Quigg*, 822 F.2d 1074, 3 USPQ 1302 (Fed. Cir. 1987) for the proposition that an expert may rely on post-filing publications to show enablement). The court also found that for those skilled in the art it was a relatively simple matter to determine whether a certain promoter would work within a specific vertebrate cell, whether a particular vertebrate cell would produce human EPO in culture, and whether a particular promoter could be operatively linked to control the transcription of the human EPO DNA. *Id.* In summary,

the court once again chose to credit Amgen's witnesses, Drs. Lodish and Wall, on the issue of enablement:

> Throughout the testimony of these witnesses, a theme becomes apparent: any challenge which one of ordinary skill in 1984 might have encountered in attempting to make and use the claimed invention using other cultured mammalian cells could be resolved by experimentation falling short of undue.

Id. at 159, 57 USPQ2d at 1515.

With these factual findings before us, TKT cannot prevail simply by reasserting in a conclusory manner that Amgen's disclosure does not enable the transformation of all mammalian or vertebrate cells or the production of human EPO. The district court carefully considered these issues, finding in the end that TKT had not met its clear and convincing burden of proof. Finding no clear error in these factual determinations, and having been directed to no legal error committed by the trial court, we will not disturb its holding that the asserted patents are not invalid for failure to meet the enablement requirement of § 112 ¶ 1.

C

Certain concerns are raised by the dissent. My brother in dissent sees the district court as having "abstained from fully inquiring" about compliance with the written description and enablement requirements of § 112, ¶ 1. In light of this strong statement, we write here to highlight what the district court did and did not do in deciding the case below. The district court should be seen as deciding the challenges to validity under each requirement as presented to it by the accused infringer. In doing so, the court fully found the facts that under-girded its conclusions on validity and relied on our case law interpreting and applying § 112. We are largely limited on review to deciding whether those findings based on that testimony are clearly erroneous and we cannot so

conclude. We may, of course, review *de novo* the court's interpretation of our precedent.

The dissent, however, does not directly challenge the court's factual findings, nor does it mention the decisions relied on by the district court. Instead, it finds fault in the absence of discussion of other precedents, namely *Eli Lilly, Gentry Gallery, In re Mayhew*, and *In re Vaeck*, and makes broader arguments seemingly based upon policy considerations.

The dissent would vacate and remand the written description issue because the district court did not cite our precedents *Eli Lilly* and *Gentry Gallery*. According to the dissent, the district court "did not focus on the correct law to be applied" and, for that reason, its "factual findings merit no deference." It is difficult to see how the district court's analysis must be rejected because it did not include discussions of these two decisions or, per the dissent, "the principles they espouse." First, it is far from clear that the defendant based its written description challenge below primarily on these two cases. Second, as we hold above, these cases are simply inapplicable here. Given these considerations, we decline to hold that the failure of the district court to cite these precedents constitutes reversible error.

In addressing the enablement inquiry the dissent looks to two other cases not discussed by the district court. It cites *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (C.C.P.A. 1976), for the proposition that "claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure." There, however, the method claims omitted a step without which the invention as claimed was wholly inoperative (meaning it simply would not work and could not produce the claimed product). *Id.* Here, the lack of a limitation directed to the exogenous expression vector in the product claims is not a failure to describe the structure of the cell or a necessary element of the claimed EPO. Once inside

the cell, the transcription control sequence and the human EPO DNA integrate randomly into the host cell chromosomes. The only required description, then, is of the EPO DNA and the transcription control sequences because it is the presence of these sequences in the cell that causes the cell to produce the EPO as claimed. Thus, the lack of a description of (or a limitation directed to) the expression vector itself (as separate from the EPO DNA and transcription control sequences) does not render the invention inoperable and therefore does not run afoul of *In re Mayhew*, 527 F.2d at 1233, 188 USPQ at 358 (affirming examiner's rejection of claims not limited to having a cooling zone at the exit of a steel strip from a zinc bath because the specification indicated that without that cooling bath the invented process would not work).

The dissent's reliance on *In re Vaeck* is also misplaced. *Vaeck* is cited for the proposition that the disclosure of one or two species (here monkey and hamster cells) "may not enable a broad genus under the circumstances." 947 F.2d at 496, 20 USPQ2d at 1444-45. But then again, it may; the inquiry is fact-specific. Here the district court held the disclosure did enable the genus because the differences between using the two described mammalian (and vertebrate) cells and other such cells were small and easily accommodated by the artisan. Thus, in assessing the evidence, the court found that the defendant's evidence fell short of clear and convincing.

But more fundamentally, we think the dissent unfairly characterizes the district court's careful and reasoned handling of the § 112 issues. The dissent repeatedly suggests that the district court "simply refused" to consider whether, having disclosed only one means to make EPO produced by vertebrate or mammalian cells, Amgen was entitled to claims for all such cells and EPO. Specifically, the dissent asserts that the district court "abstained" from considering whether the absence of a claim limitation on the means of expression

raises § 112 issues.[11] We find this hard to understand. The district court explicitly analyzed these requirements in addressing defendant's specific challenges to validity. It decided they were not proven sufficiently and its decision is supported both by citations to our precedent and its own factual findings. Thus, rather than refusing to answer the § 112 questions, it seems the district court did answer them affirmatively.

In addressing this specific issue, the district court relied principally on two of our precedents: *Phillips Petroleum* and *Cellpro*. The court construed the former as not requiring the written description to include later-developed methods for making a claimed product. *Amgen*, 126 F. Supp. 2d at 150, 160, 57 USPQ2d at 1508, 1515. The court construed the latter as holding that a product claim is supported by adequate written description and enabling disclosure even if it describes only one method of making the claimed product. *Id.* at 160, 57 USPQ2d at 1515. These cases have not been shown to be incorrectly applied by the district court. And we, like the district court, are obligated to follow them both, as they explicitly support the court's rulings. *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465 (holding that the patentee was entitled to a prior filing date because the earlier disclosure of polypropylene as known at that time described and enabled a later claim to "[n]ormally solid polypropylene" even though a new, higher molecular weight form of polypropylene had been subsequently discovered), and *Cellpro*, 152 F.3d at 1361, 47 USPQ2d at 1719 (affirming summary judgment of enablement of a product claim over a challenge that two alternative embodiments disclosed in the patent were not enabled because "the enablement requirement is met if the description enables any mode of making and using the invention").

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[11] In this same vein, the dissent suggests that our court here has somehow "waived" the requirements of § 112 for product claims.

Rather than addressing these precedents, the dissent makes broad arguments that are not specifically grounded in our precedent. The dissent asks whether Amgen's disclosure "entitles it to claim *all* EPO produced by mammalian cells in culture, or *all* cultured vertebrate cells that produce EPO." (emphasis in original). While this broad entitlement question may be important as a policy matter, where, as here, we have applicable precedents, we are bound by the specific inquiries they mandate. Here, we, as did the district court, look to the requirements of § 112 as interpreted by our precedent. In short, the district court cannot have committed legal error by faithfully following controlling precedent of this court.

Lastly, the dissent emphasizes that omissions in the claim limitations and in the disclosures of the specifications "raised enablement issues." If the claims were still in prosecution before the PTO, perhaps the examiner could make an issue of such omissions. The dissent talks of what is "essential for the *patentability* of the claims." (emphasis added). But the question here is not patentability of application claims, but validity of issued claims that are presumed valid by statute. Now a heavy burden falls on the challenger. The district court found that the challenger had not carried that burden. It admitted that the questions were close—indeed, it found invalidity proven, but only by a preponderance. Hence, rather than refusing to decide questions of validity under § 112, it did decide them under the proper standard of proof. We see no reversible error.

III

Having addressed the claim interpretation and § 112 issues, we move to the second step of the infringement analysis: comparison of the properly construed claims to the accused product or process. *See, e.g., CCS Fitness*, 288 F.3d at 1365, 62 USPQ2d at 1662. Our review of this step differs depending upon whether the issue of infringement was resolved on summary judgment or after a full trial. *See Cole v. Kimberly-*

Clark Corp., 102 F.3d 524, 528, 41 USPQ2d 1001, 1004 (Fed. Cir. 1996). In the case of summary judgment, as with claim 1 of the '422 patent, we review *de novo* the trial court's finding that there was no genuine issue as to any material fact regarding infringement. *Id.*, 41 USPQ2d at 1004; Fed. R. Civ. P. 56(c). After a full bench trial, infringement is a question of fact that we review, of course, for clear error. *Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1363, 53 USPQ2d 1892, 1895 (Fed. Cir. 2000). When JMOL is entered under Fed. R. Civ. P. 52(c), as with the '698 and '080 patents, we review the district court's determination for clear error, as if it had been entered at the close of all the evidence. *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1643 (Fed. Cir. 2000). Anchored in the proper scope of review for each claim in dispute, we now address the trial court's infringement analysis.

A. The '933 Patent

Amgen asserted the following three claims of the '933 patent against TKT:

> 1. A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.
>
> 2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.
>
> 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Critical for our purposes is the final limitation of claim 1, which states that the claimed glycoprotein has "glycosylation which differs from that of human urinary erythropoietin." Glycosylation is the addition of carbohydrate side chains to amino acid residues in protein sequences to form glycoproteins. *Encyclopedia of Molecular Biology* at 1047. At the *Markman* hearing, Amgen asserted that the phrase meant "the attached carbohydrate groups differ when analyzed by standard prior art techniques known as of 1983-84." TKT argued, by contrast, that it meant "the carbohydrate groups attached to side chains of the erythropoietin polypeptide backbone differ by Western blot analysis and SDS/PAGE and carbohydrate composition analysis from those of human urinary erythropoietin to at least the degree described in the patents-in-suit."

Thus, the primary difference concerned which, if any, techniques were acceptable to determine whether the glycosylation was different. The district court found that the examples in the specification teach three measurement methods, but that they failed to limit "glycosylation which differs" to those methods. The court ruled, therefore, that the phrase means: "Glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." *Amgen*, 126 F. Supp. 2d at 91-92, 57 USPQ2d at 1463.

It is undisputed that in 1983, there were at least two analytical techniques available for detecting differences in glycosylation between two glycoproteins. SDS-PAGE is a type of gel electrophoresis in which the glycoprotein of interest is bound to a charged compound that denatures the glycoprotein, which in turn is subjected to an electric field; glycoproteins of different molecular weight (reflecting their different glycosylations) will migrate through the electric

field at different speeds. *Id.* at 124, 57 USPQ2d at 1488. Isoelectric focusing ("IEF"), a second technique known to artisans in 1983, is similar to SDS-PAGE except that it determines the pH at which a protein is electrically neutral because the charge is placed in the gel in the form of a pH gradient, rather than on the glycoprotein itself. *Id.* at 125, 57 USPQ2d at 1488. The data obtained by both these methods can be visualized by Western blot, allowing an approximation of the molecular weight.

There was little dispute that any of these tests could be used to determine the glycosylation of a glycoprotein. Indeed, the district court noted that the testimony of an Amgen witness, Dr. Cummings, "would discharge Amgen's duty of showing by a preponderance of the evidence that HMR4396 has glycosylation which differs from that of human urinary EPO." *Id.* at 127, 57 USPQ2d at 1490. However, the court also credited evidence that indicated two uEPO preparations produced from the same batch of starting materials could nevertheless have different glycosylation patterns. *Id.* at 129, 57 USPQ2d at 1492 ("[A] skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification methods could have different glycosylation. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target."). Consequently, because the district court concluded that the patent failed to identify a single standard by which the "difference" could be measured, it held that TKT did not infringe and the '933 patent was invalid for failure to satisfy 35 U.S.C. § 112:

> The claim language of the '933 patent, however, presupposes that the glycosylation of urinary erythropoietin is a fixed, identifiable marker against which the glycosylation of recombinant EPOs can be measured. Yet, how can one prove that a recombinant EPO has glycosylation which differs from that of urinary EPO when the glyco-

> sylation of urinary EPO itself varies? The Court need not answer this conundrum. All that need be said is that Amgen's showing that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs is insufficient to carry its burden of proving infringement by a preponderance of the evidence that TKT infringes the claim limitation.

Id. at 129, 57 USPQ2d at 1492.

Amgen argues on appeal that an ordinarily skilled artisan in 1984 would have understood, based upon the patent disclosure, that there were two principal processes for purifying uEPO, with the technique taught by Miyake (SDS-PAGE) recognized as the standard. It asserts that it carried its burden of proving infringement because its empirical evidence "unequivocally demonstrated the glycosylation difference between Miyake-purified uEPO and the accused product." But it seems to us that Amgen has failed to address the trenchant question on this issue, *i.e.*, whether uEPO is necessarily glycosylated in the same way. Amgen deals rather cavalierly with the question in both its principal and reply brief, stating summarily that the district court erred and suggesting that the question is unimportant.

By definition, one must know what the glycosylation of uEPO is with certainty before one can determine whether the claimed glycoprotein has a glycosylation different from that of uEPO. In its discussion characterizing recombinant glycoprotein products, the specification of the '933 patent does not direct those of ordinary skill in the art to a standard by which the appropriate comparison can be made. *See* '933 patent, col. 28, line 33 - col. 29, line 7. The district court considered evidence that experiments conducted by Amgen in 1984 showed that different urinary EPO preparations had different glycosylation. For example, EPO purified from the urine of a single patient ("Lot 82") using a modified Miyake procedure was shown to have a different glycosylation from

other human uEPO (taken from Goldwasser). *Amgen*, 126 F. Supp. 2d at 129, 57 USPQ2d at 1491-92. And so, even assuming that Amgen is correct that one of ordinary skill in the art would have understood the benchmark test for glycosylation to be Miyake, its contention still fails. As the district court noted, the Miyake article provides a method of purification, but hardly suggests uniformity of glycosylation of the human uEPO studied:

> The 1977 Miyake et al. publication, for example, describes the purification from the same starting material of two homogeneous urinary EPO preparations (Fraction II and Fraction IIIA) that had about the same potency in terms of biological activity. Fractions II and IIIA . . . had different carbohydrate compositions and, therefore, differed from each other in glycosylation. Thus, these two uEPO preparations, though produced by the same procedure (*Miyake) and derived from the same batch of starting material, nonetheless had different glycosylation.

Id. at 129, 57 USPQ2d at 1491; *see also* Miyake, *Purification of Human Erythropoietin*, J. Bio. Chem. 5558, 5562 (1977) ("In spite of our finding of similar potency and molecular size, these two preparations [Fractions II and IIIA] must be considered different. The chemical basis for this difference is now being studied."). Amgen fails to controvert or otherwise address this evidence in its cross-appeal.

Under 35 U.S.C. § 112 ¶ 2, a patent applicant is required, at the close of his specification, to "particularly point[] out and distinctly claim[] the subject matter the applicant regards as his invention." The requirement of claim definiteness set out in § 112 ¶ 2 assures that claims in a patent are "sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). The standard of indefiniteness is somewhat high; a claim is not indefinite merely because its scope

is not ascertainable from the face of the claims. *Cf., e.g., LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc.*, 275 F.3d 1347, 1359-60, 61 USPQ2d 1193, 1202 (Fed. Cir. 2001) (affirming district court finding that patent was not indefinite, despite testimony from a co-inventor that he did not understand what the claim limitation "substantially completely wetted" meant). Rather, a claim is indefinite under § 112 ¶ 2 if it is "insolubly ambiguous, and no narrowing construction can properly be adopted." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001); *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349, 63 USPQ2d 1769, 1776 (Fed. Cir. 2002) ("It is not our function to rewrite [indefinite] claims to preserve their validity."). Applying these legal maxims to the facts of this case, we agree with the district court that the claims requiring "glycosylation which differs" are invalid for indefiniteness.

We find erroneous, however, its conclusion that invalidity for indefiniteness should be found only in the alternative. A claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1378, 55 UPQ2d 1279, 1282 (Fed. Cir. 2000) (citing *Personalized Media Comm., LLC v. ITC*, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998)). So it is here. Recognizing that it was faced with a "conundrum" regarding claim construction, the court held that the patent was not infringed because Amgen could not meet its burden simply by showing "that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs." *Amgen*, 126 F. Supp. 2d at 129, 57 USPQ2d at 1492. That the court recognized that one of ordinary skill in the art would have been faced with this "conundrum" should have ended the inquiry, for such ambiguity in claim scope is at the heart of the definiteness requirement of 35 U.S.C. § 112 ¶ 2. One cannot logically determine whether an accused product

comes within the bounds of a claim of unascertainable scope. Accordingly, the finding that TKT does not infringe the '933 patent is vacated and the finding that the '933 patent is invalid under § 112 is affirmed.

B. The '080 Patent

Claims 2-4 of the '080 patent are at issue:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.
>
> 3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.

The critical limitation of the asserted claims in the '080 patent is the requirement that the erythropoietin glycoprotein "comprise[] the mature erythropoietin amino acid sequence of Fig. 6." The court construed the claim term "mature erythropoietin amino acid sequence of Figure 6" that appears in claims 4 and 6 of the '698 patent and claims 2 and 4 of the '080 patent. The dispute here arises out of a mistake in the specification. At the time the patent was drafted, it was believed that the sequence included 166 amino acids, and this belief is depicted in Figure 6. In fact, later research demonstrated that the full sequence was actually *165* amino acids; the last (arginine) is actually cleaved off prior to the

protein's secretion from the cell. Amgen argued that the reference to Figure 6 was irrelevant, even if the figure had too many amino acids, because it still showed the "mature [i.e., 165] erythropoietin amino acid sequence." TKT argued that the reference to Figure 6 required the term to be construed as depicted in Figure 6, and thus with 166 amino acids. Following trial,[12] the court adopted TKT's proposal, relying on what it considered key language in the specification supporting that construction: "Fig. 6 thus serves to identify the primary structural conformation (amino acid) sequence of mature human EPO as including 166 specified amino acid residues . . . ." '080 patent, col. 12, lines 3-5. *Amgen*, 126 F. Supp. 2d at 86-87, 57 USPQ2d at 1459.

In total, Figure 6 consists of five separate figures denominated Figs. 6A through 6E, which collectively disclose the sequence of human genomic EPO DNA and the encoded EPO. The detailed description in the '080 patent indicates that the specificity of Figure 6 is not to be lightly disregarded:

> Fig. 6 thus serves to identify the primary structural conformation (amino acid sequences) of mature human EPO as including 166 specified amino acid residues (estimate M.W.=18,399). Also revealed in the Figure is the DNA sequence coding for a 27 residue leader sequence along with 5' and 3' DNA sequences which may be significant to promoter/operator functions of the human gene operon. Sites for potential glycosylation of the mature human EPO polypeptide are designated in the Figure by asterisks. It is worthy of note that the specific amino acid sequence of Fig. 6 likely constitutes that of a naturally occurring allelic form of human erythropoietin. Support for this position is found in the results of

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[12] The court declined to rule on this issue at the *Markman* hearing, instead choosing to take the matter under advisement. See 126 F. Supp. 2d at 87, 57 USPQ2d at 1459.

> continued efforts at sequencing of urinary isolates of human erythropoietin which provided the finding that a significant number of erythropoietin molecules therein have a methionine at residue 126 as opposed to a serine as shown in the Figure.

'080 patent, col. 21, lines 29-40.

When the district court revisited the "Figure 6" issue, it concluded that the language of the claims, read in conjunction with the portion of the specification excerpted above, clearly identified the mature erythropoietin amino acid sequence as exactly depicted in Figure 6. In so doing, the court expressly rejected Amgen's contention that the claim should be read as covering the mature amino acid sequence, of erythropoietin, whatever its number of amino acids. *Amgen*, 126 F. Supp. 2d at 100, 57 USPQ2d at 1470 ("Had Amgen claimed only 'the mature erythropoietin amino acid sequence' without associating or linking that amino acid sequence to Figure 6 its argument that its claims cover whatever sequence (whether it contained 165 or 166 amino acids) is ultimately secreted by the cell might have more momentum."). The district court therefore found at the close of Amgen's case that HMR4396 does not literally infringe the asserted claims of the '080 patent.

The issue of infringement under the doctrine of equivalents was much closer, and likewise centered on the "Figure 6" limitation.[13] The district court concluded that Amgen had proven by a preponderance of the evidence that the 165 amino acid sequence satisfied the function-way-result test, crediting in particular the testimony of Dr. Lodish that TKT's

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[13] The district court held that every other limitation of the asserted claims in the '698 patent were met literally by the accused product/process. *Amgen*, 126 F. Supp. 2d at 132-33, 57 USPQ2d at 1493. Thus, whether equivalent infringement occurred turned on whether the "Figure 6" limitation was equivalently met.

missing arginine residue (the 166th amino acid appearing in Figure 6) does not affect the *in vivo* biological activity of its EPO product. *Id.* at 133, 57 USPQ2d at 1495. In reaching its conclusion, the court rejected TKT's argument that Amgen was not entitled to any range of equivalents under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 234 F.3d 558, 566, 56 USPQ2d 1865, 1870 (Fed. Cir. 2000), because during prosecution it had narrowed the scope of the claim for reasons related to patentability. The parties have cross-appealed on this patent, with Amgen asserting that the district court erred by finding no literal infringement and TKT continuing to press its estoppel theory as a basis for denying any range of equivalents.

Naturally, Amgen continues to focus on the "mature" portion of the relevant claim limitations to support its argument that the trial court erred by finding no literal infringement. According to Amgen, the practical result of the trial court's conclusion is to read out from the claims the preferred embodiment of the invention because the specification makes clear that "mature" human EPO is that form which circulates in the blood, *i.e.*, the 165 amino acid form that has already been secreted. This argument strains reason to its breaking point; our reading of the patent, like the district court's, will support no such interpretation.

Amgen's argument is based upon a misconstruction of the term "including" that evinces a misunderstanding of the plain meaning of that term, as well as the term "comprise," which appears in the '080 patent claims.[14] "Comprising is a term of

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[14] Amgen argues: "The specification describes the mature amino acid sequence of human EPO as 'including'—not 'limited to'—the 1-166 sequence. Properly construed, Lin's claimed sequence—the mature sequence—includes the fully processed form of any glycoprotein having the Figure 6 sequence. That includes both the 1-165 and the 1-166 amino acid sequences of Figure 6. Only this construction affords 'mature' its proper meaning, and includes Lin's preferred embodiment."

art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1633 (Fed. Cir. 1997). The word "include" means the same thing. *See Hewlett-Packard Co. v. Repeat-O-Type Stencil Mfg. Corp., Inc.*, 123 F.3d 1445, 1451, 43 USPQ2d 1650, 1655 (Fed. Cir. 1997) ("The claim term 'including' is synonymous with 'comprising,' thereby permitting the inclusion of unnamed components."); *see also Webster's II New Riverside University Dictionary* 619 (1984) ("*include*: 1. To have or take in as a part or member: CONTAIN; 2. To put into a group class, or total."). Thus, a claim reciting "a widget comprising A and B," for example, would be infringed by any widget containing A and B, no matter that C, D, or E might be present.

If, then, as the specification states, "the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues," it is simply illogical for Amgen to argue that that means anything other than, at minimum, the 166 amino acids shown in Figure 6. This is verified by the fact that '080 claims 2 and 3 claim an erythropoietin glycoprotein "*compris[ing]* the mature erythropoietin amino acid sequence of Fig. 6 . . . ." Again, read properly in light of the term "comprising," this means that the claimed glycoprotein must have—at minimum—all 166 amino acids shown in Figure 6.

Turning to the finding of infringement under the doctrine of equivalents, TKT asserts that Amgen should be estopped from obtaining such coverage under *Festo*. Specifically, TKT alleges that the "mature amino acid sequence of Figure 6" limitation that appears in the '080 patent was added to overcome a double-patenting rejection, and therefore constitutes an amendment related to patentability. We agree.

The district court correctly found that the amendment, although voluntary, was made to avoid a "same invention" double patenting rejection, *Amgen*, 126 F. Supp. 2d at 135, 57 USPQ2d at 1496, and although the Supreme Court reversed our decision in *Festo* and rejected the notion of an absolute bar to the doctrine of equivalents, it agreed with our holding "that a narrowing amendment to satisfy any requirement of the Patent Act may give rise to an estoppel." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 122 S. Ct. 1831, 1839 (2002). Contrary to the district court's conclusion, "'[s]ame invention' double patenting is based upon 35 U.S.C. § 101, which states that an inventor may obtain 'a patent' for an invention." *In re Lonardo*, 119 F.3d 960, 965, 43 USPQ2d 1262, 1266 (Fed. Cir. 1997) (emphasis added). Therefore, the district court's finding of equivalent infringement of the '080 patent is vacated and remanded for an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel. *Festo*, 122 S. Ct. at 1839.

C. The '698 Patent

The '698 patent is directed generally to a process for producing a glycosylated erythropoietin polypeptide. Claims 4-9 are at issue. Independent claims 4 and 6 read as follows:

> 4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

> 6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

Infringement of dependent claims 5 and 7-9 rises or falls with the analysis that applies to independent claims 4 and 6.[15] The phrase "operatively linked" appears in claim 4 of the '698 patent, and is related by dependency to claims 5 and 9. According to the district court, the phrase relates to the relationship between promoter DNA and the DNA that is transcribed downstream from the promoter DNA. Amgen contended that the phrase means "positioned such that it provides for initiation of transcription of a gene." TKT argued that the term means positioned adjacent "to the DNA encoding EPO in a way that maintains the capability to initiate transcription of EPO DNA." In other words, Amgen argued that the words "operatively linked" imposed no spatial restriction, whereas TKT contended that because the patent allegedly taught placing the promoter DNA immediately adjacent to the DNA encoding EPO, the term "operatively linked" ought be limited

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[15] Claim 5 claims "[t]he process of claim 4 wherein said promoter DNA is viral promoter DNA." Claim 7 claims "[th]e process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA." Claim 8 claims "[t]he process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA." And claim 9 claims "[t]he process according to claims 2, 4 and 6 wherein said cells are mammalian cells."

by location. The district court held that the term "operatively linked" means "the promoter DNA is linked to the EPO DNA is such a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen*, 126 F. Supp. 2d at 90, 57 USPQ2d at 1462.

The district court granted TKT summary judgment of non-infringement of independent claims 4 and 6 (and hence dependent claims 5 and 7-9) of the '698 patent because it found that Amgen had failed to carry its Rule 52(c) burden. *Id.* at 102, 57 USPQ2d at 1471. Amgen assails this conclusion as not in accordance with law, inasmuch as the differences considered dispositive by the district court are not claimed and thus have no bearing on a proper infringement analysis. In fact, according to Amgen, the district court neglected to identify any limitation of the '698 patent that the accused process fails to literally meet, and also failed to explain why, in the absence of literal infringement, those limitations were not otherwise equivalently met. We agree with Amgen, and therefore conclude *vacatur* is appropriate.

The district court properly recognized that the infringement analysis of process claims is necessarily different from that for product claims. *See id.* at 102, 57 USPQ2d at 1471 ("The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything."). But after a correct discussion of the differences in the infringement analysis, the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment. *Id.* ("Based on . . . *the many differences between Amgen's and TKT's processes* . . . Amgen's proof of infringement on the '698 patent [is] insufficient . . . .") (emphasis added).

For example, the court concluded that a fundamental distinction between the respective processes was that TKT employs homologous rather than heterologous recombination, whereas "[i]n order to make EPOGEN®, Amgen transfects [CHO] cells with a vector that contains both viral promoter DNA and the human EPO gene." *Id.* This clear reference to the preferred embodiment of Example 10, which the district court considered "the process most heavily relied upon by Amgen in its patent," *id.* at 103, 57 USPQ2d at 1472, misses the point that none of the claims at issue contain such a limitation. And apart from the limitations of the asserted claims, the differences in the two processes are wholly irrelevant to the infringement analysis.

The district court likewise found material the fact that TKT places its promoter and enhancer farther upstream than does Amgen. In light of the court's claim construction, however, it would seem TKT satisfies the "operatively linked" limitation, as there is no question that TKT's promoter causes its intended functional effect. In any event, the trial court once again compared the accused process by reference to an example rather than the *claimed* process:

> As explained in Example 7 and illustrated in Figure 4, Amgen created the vector by cleaving, with BstEII restriction endonucelases . . . 'at a position which is 44 base pairs 5' to the initiating ATG coding for the pre-peptide and approximately 680 base pairs 3' to the HindIII restriction site' . . . . TKT's process has within the DNA sequence upstream of the codons that express the EPO polypeptide several ATG sites . . . . The court finds that such a process is sufficiently different from that encompassed by Amgen's invention that judgment of non-infringement should follow.

Id.

Again, this was legal error insofar as the infringement analysis is not tied to the asserted claims. We therefore vacate and remand so that the court may conduct a proper infringement inquiry in the first instance, comparing the accused device to the properly construed claims without limiting their scope to the examples in the specification or other limitations that are not properly a part of claims 4-9.

D. The '422 Patent

Claim 1 of the '422 patent, the only one in dispute, claims "[a] pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." In the *Markman* hearing, Amgen contended the phrase "purified from mammalian cells grown in culture" meant "purified from the in vitro culture in which the mammalian cells have been grown," whereas TKT argued that it meant "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media." Concluding that TKT's construction would exclude the patent's preferred embodiment (Example 10), the court read the phrase "mammalian cells grown in culture" as a whole to encompass purification techniques from the cells or the cell culture medium. *Id.* at 88-89, 57 USPQ2d at 1460-61. As indicated earlier, the district court immediately turned to and granted Amgen's motion for summary judgment of infringement of the '422 patent at the close of the *Markman* hearing.

According to the district court, it was clear from the beginning that the accused product met most limitations of claim 1. That HMR4396 was a pharmaceutical composition that contained a therapeutically effective amount of human erythropoietin was plain, in view of the Investigational New Drug Application ("INDA") that TKT filed with the Food and Drug Administration. *Id.* at 94-95, 57 USPQ2d at 1465. The

district court further concluded that HRM4396 contained "a pharmaceutically acceptable diluent, adjuvant or carrier" in view of the testimony of TKT's Rule 30(b)(6) designee, who testified that the HRM4396 recovered in bulk from the culturing of human cells was diluted with a phosphate buffer to control the pH and provide a product of desired strength. *See id.* at 95, 57 USPQ2d at 1466. The sole remaining issue, then, was whether the accused product was "purified from mammalian cells grown in culture." Rather than taking the utterly untenable position that humans are not mammals, TKT conceded infringement under the court's claim construction. *Id.* at 95, 57 USPQ2d at 1466.

TKT tries three different tactics on appeal to escape this concession of infringement. First, TKT argues that "mammalian cells," as the phrase is used in the '422 patent, do not include its cells because Amgen excluded the use of human cells to produce human EPO from its invention. Second, TKT asserts that the finding of infringement was in error because the patent specification defines pharmaceutical compositions "as comprising 'polypeptides of the invention'," and HRM4396 is not a "polypeptide of the invention" inasmuch as the invention is "uniquely characterized" by (and hence limited to) exogenous EPO DNA. Finally, TKT challenges the finding of infringement because, it asserts, the intrinsic evidence limits the phrase "purified from mammalian cells grown in culture" to purification that takes place inside the cells, and not—like TKT—from the culture media.[16] As infringement of the '422 patent was granted on summary judgment, we review the district court's conclusion *de novo*, applying the same standard applied by the trial court. *Schering Corp. v. Amgen, Inc.*, 222 F.3d 1347, 1351, 55

[16] The basis for this argument is that claim 2 of the '698 patent recites recombinant EPO "isolated from the host cell or the medium of its growth." Therefore, asserts TKT, "Amgen also knew how to claim what it now seeks, but failed to do so."

USPQ2d 1650, 1653 (Fed. Cir. 2000). Under this standard, we agree with the trial court that a grant of summary judgment of infringement of the '422 patent was warranted.

We cannot accept, for the reasons already stated, TKT's proposed reading of the claim term "mammalian" and its attempt to import the term exogenous into the claims; we therefore reject out of hand the contention that Amgen expressly excluded the use of human cells to express EPO and the use of endogenous DNA from the scope of its invention. Thus, the issue resolves to a narrow one: the accused product, HRM4396, infringes '422 patent claim 1 unless TKT is correct that the claim limitation "purified from mammalian cells grown in culture" means that the EPO product must be recovered directly from the cell, and not from the culture medium.

At the *Markman* hearing, Amgen contended the phrase means "purified from the in vitro culture in which the mammalian cells have been grown"; TKT argued that it means "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media. The trial court read the phrase to encompass purification techniques from the cells or the cell culture medium because to do otherwise, it found, would exclude the patent's preferred embodiment as disclosed in Example 10. *Amgen*, 126 F. Supp. 2d at 88-89, 57 USPQ2d at 1461.

Example 10 "describes expression systems employing Chinese hamster ovary (CHO) DHFR$^-$ cells and the selectable marker, DHFR." '422 patent, col. 25, lines 38-40. As a part of the description, the example discloses that gene amplification in cell culture media is possible to increase productivity of the targeted recombinant EPO product. After describing an example of such a gene amplification system, the specification goes on to state: "The productivity of the EPO producing CHO cell lines described above can be improved by appropriate cell culture techniques. The propagation of

mammalian cells in culture generally requires the presence of serum in the growth media. *A method for production of erythropoietin from CHO cells in media that does not contain serum greatly facilitates the purification of erythropoietin from the culture media." Id.*, col. 27, lines 8-14 (emphasis added). We agree with the district court that this disclosure—the undisputed preferred embodiment of the invention—contemplates purification of erythropoietin from the culture media. *See also* '933 patent, col. 28, lines 28-32 ("Mammalian cell expression products may be readily recovered *in substantially purified form from culture media* using HPLC (C4) employing an ethanol gradient, preferably at pH7." (emphasis added)).

TKT does not challenge the district court's conclusion regarding the disclosure of Example 10. Accordingly, TKT's challenge ultimately must fail unless we read the preferred embodiment out of the claims, but rare is the case where we should or will do so. A claim interpretation that reads out a preferred embodiment "is rarely, if ever, correct and would require highly persuasive evidentiary support." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1578 (Fed. Cir. 1996). We have done so only one time—in an instance where the patent applicant limited the full scope of the claim language to omit the preferred (and only disclosed) embodiment in order to overcome an examiner's rejection. *See Elektra Instr. S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1308, 54 USPQ2d 1910, 1914 (Fed. Cir. 2000). The present case lacks the "persuasive evidentiary support" necessary for us to read the claims so as to exclude the preferred embodiment disclosed in Example 10; we therefore decline to do so.

E. The '349 Patent

The '349 patent contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

> 1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin.
>
> 3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.
>
> 6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Each of the claims contain the limitation "non-human DNA sequences that control transcription" that appears in claim 1 of the '349 patent or the limitation "transcriptional control DNA sequences, other than human erythropoietin transcription control sequences" that appears in claim 4 of the '349

patent. Transcription is the process whereby RNA polymerase copies genetic information contained in a DNA nucleotide sequence into an RNA sequence. It is a critical step in the expression of proteins like erythropoietin and is itself controlled by specific DNA sequences. According to the patent, "transcription control sequences" is the collective term for DNA sequences that not only "provide a site for initiation of transcription into mRNA," but also are capable of binding proteins that determine "the frequency (or rate) of transcriptional initiation." '349 patent, col. 2, lines 3-12.

Amgen contended that this phrase means "non-human DNA sequences that are able to initiate or regulate RNA synthesis from EPO DNA." TKT argued that the phrase means "DNA sequences which did not originate in the human genome, which initiate and regulate RNA synthesis of adjacent DNA, and which replace the human EPO transcription control sequences." By including the term "adjacent DNA" in its construction, TKT sought to require the DNA sequences that control transcription to be located in a position adjacent to the gene segment intended to be expressed. Furthermore, TKT contended that in order to "control" transcription, the DNA sequences must both initiate and regulate the transcription of a gene. Amgen objected to the use of "and," preferring a construction that required DNA sequences either to initiate or regulate transcription. Finally, the parties disagreed as to the meaning of "non-human." Amgen argued that "non-human" means "not part of the human genome," whereas TKT contended it meant "not originating in the human genome."[17]

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[17] The importance of this distinction is that, because it is scientifically arguable that viral DNA originates in the human genome, the viral promoter DNA that TKT employs thus might not fall within the meaning of the claim.

First, the court rejected TKT's position and concluded that "non-human" DNA sequences are DNA sequences that are "not part of the human genome." The court similarly rejected TKT's "adjacent" language because "no claim term could reasonably be construed to be limiting the transcription control DNA sequences by their location." Finally, the court held that DNA sequences that control transcription are DNA sequences that initiate and regulate the processes of transcription. *Amgen*, 126 F. Supp. 2d at 88, 57 USPQ2d at 1459-60.

The district court entered judgment of noninfringement for TKT on method claim 7 of the '349 patent under an identical rationale to that used to grant judgment of noninfringement for the method claims of the '698 patent. *Id.* at 122, 57 USPQ2d at 1486. As we have found the court's analysis with respect to the '698 patent to be legally unsupportable, *see supra* at 41-42, we likewise vacate the district court's judgment with respect to claim 7 of the '349 patent and remand for further consideration. As to the product claims of the '349 patent, the court held that each of claims 1, 3, 4, and 6 were literally infringed, and further held (alternatively) that claims 3 and 6 were equivalently infringed.[18]

Aside from the challenge, already rejected, to the trial court's construction of the term "vertebrate cells," TKT

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[18] We note also that the trial court granted summary judgment of infringement of the product claims of the '349 patent. It modified its summary judgment finding (but reached the same result) with respect to the "controlling transcription" limitation in light of extensive trial testimony. *Amgen*, 126 F. Supp. 2d at 118, 57 USPQ2d at 1485. Accordingly, unlike the other limitations in the '349 patent, we review the court's conclusion with respect to "controlling transcription" for clear error, even though it comes to us from a grant of summary judgment of infringement. Because TKT has not demonstrated clear error in the trial court's conclusion, we affirm the finding of infringement.

mounts a weak challenge to these findings of infringement apparently under the reverse doctrine of equivalents.[19]

Under the reverse doctrine of equivalents, an accused product or process that falls within the literal words of a claim nevertheless may not infringe if the product or process "is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way." *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 339 U.S. 605, 608-09, 85 USPQ 328, 330 (1950); *see generally* Donald S. Chisum, 5A CHISUM ON PATENTS §-18.04 (1999). This doctrine is equitably applied based upon underlying questions of fact, *see Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1581, 18 USPQ2d 1001, 1013 (Fed. Cir. 1991), when the accused infringer proves that, despite the asserted claims literally reading on the accused device, "it has been so changed that it is no longer the same invention." *Del Mar Avionics, Inc. v. Quinton Instr. Co.*, 836 F.2d 1320, 1325, 5 USPQ2d 1255, 1259 (Fed. Cir. 1987) (citing *Graver Tank*, 339 U.S. at 608-09).

We are not persuaded by TKT that this is a case where equity commands a determination of non-infringement despite its product literally falling within the scope of the asserted claims. TKT relies on findings of the district court regarding differences in the way the accused device controls transcription in the '698 patent. It is true, as Amgen candidly admits, that the method by which TKT controls transcription is not identical. Whereas the patent describes placing the

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[19] The sum total of TKT's challenge to the infringement finding, aside from the "vertebrate" issue, is as follows: "[TKT] also do[es] not use the 'transcription control sequences' of the '349 patent. As the court found, [TKT]'s transcription control sequences are not only structurally different from Amgen's sequences but also function in a different way. Because of those differences in structure and function, [TKT] do[es] not infringe the 'transcription control sequences' limitation in the '349 claims."

promoter DNA in close proximity, or even adjacent, to the EPO leader peptide, TKT places its promoter further upstream. But again, it is error to conduct infringement analyses in a vacuum, without reference to the claims at issue.

The vertebrate cells of the '349 patent, as claimed, are comprised of non-human DNA sequences that control transcription of DNA encoding human erythropoietin. And "control[ling] transcription of DNA encoding human erythropoietin" simply means initiating and regulating the process of transcription. *Amgen*, 126 F. Supp. 2d at 88, 57 USPQ2d at 1460. This limitation is met literally because the cytomegalovirus in TKT's R223 cells performs this function, *id.* at 118, 57 USPQ2d at 1484, notwithstanding TKT's reliance on the court's erroneous analysis of the '698 patent method claims.

IV

Our affirmance of the district court's findings that certain of the asserted claims are infringed is not yet the coup de grâce for TKT; non-frivolous validity issues remain. One of the statutory requirements for patentability is that the invention for which a patent is sought was not known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention by the applicant. *See* 35 U.S.C. § 102(a). Similarly, one is not entitled to a patent if the subject matter of the invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the invention is directed. *See id.* § 103. TKT relies particularly on two items of prior art that allegedly render certain of the asserted claims anticipated under § 102(a) or obvious under § 103. We discuss each in turn.

A

TKT contends the asserted claims are anticipated by the work of Dr. Eugene Goldwasser ("Goldwasser"). Beginning

in 1979-80, Goldwasser conducted a clinical study at the University of Chicago at Illinois in which he obtained a preparation of highly purified erythropoietin derived from human urine and administered approximately 10,000 units of human urinary EPO to three anemic patients. *Amgen*, 126 F. Supp. 2d at 111, 57 USPQ2d at 1478. Although this study showed an increase in reticulocyte count in all three patients, and an increase in erythroid cells, plasma iron clearance rate, and red cell mass in at least one patient, Goldwasser admitted that "[t]here was no significant change in hematocrit in any patient." *Id.* at 111-12, 57 USPQ2d at 1478. And because there was no increase in hematocrit, Goldwasser testified in his deposition that he considered the study a failure. The district court concluded, as a result, that the study could not be invalidating anticipatory prior art: "[A]nother's experiment, imperfect and never perfected will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it." *Id.* at 112, 57 USPQ2d at 1479 (quoting *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1558, 225 USPQ 26, 33 (Fed. Cir. 1985)).

The district court similarly concluded that Goldwasser did not render the patents obvious. Of paramount importance to the court was the fact that the prior art references, including Goldwasser, lacked Amgen's disclosure of the genetic sequence of EPO and failed to describe any transcription control sequences. *Id.* at 115, 57 USPQ2d at 1481. The court also considered the secondary factors—particularly long-felt need and commercial success—to be of high importance. *Id.* at 116, 57 USPQ2d at 1482 ("Before the advent of Amgen's product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known. Furthermore, Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world. As a result, Dr. Lin received widespread public acclaim for his work.").

TKT assigns error to the district court's alleged blind acceptance of Goldwasser's assertion that the test was a failure without considering the contemporaneous testimony of Goldwasser's collaborator, Dr. Baron, who reported to the Food and Drug Administration in 1984 that evidence of erythroid marrow stimulation was detected. In particular, according to TKT, the court erred by failing to "look[] at the definition of therapeutic effect in the specification." We agree that "therapeutically effective" must be defined in accordance with *Markman v. Westview Instruments* before this issue can be properly resolved, and we therefore vacate and remand for further proceedings with respect to Goldwasser.

For the *Markman* hearing in this case, ten terms were "pre-selected" based upon their relationship to Amgen's then-pending motion for summary judgment of infringement. *Id.* at 81, 57 USPQ2d at 1455. Whether those "pre-selected" terms were chosen by the court or the parties is unclear from the record, but what is clear is that "therapeutically effective" was not among them. And so the district court, assumedly viewing "therapeutically effective" as not in dispute, construed it in its discussion of the Goldwasser reference:

> Such evidence [of, e.g., increased erythroid marrow stimulation] should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged. *Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness*, Dr. Goldwasser's study, which revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO.

Id. at 112, 57 USPQ2d at 1479 (second emphasis ours). Had "therapeutically effective" not been in dispute, no error would arise. A district court may—indeed, often must—interpret or define a term in the claims that is not in dispute in order to

provide a proper context for the discussion of the terms that are in dispute. *See, e.g., DeMarini Sports v. Worth, Inc.*, 239 F.3d 1314, 1323, 57 USPQ2d 1889, 1893-94 (Fed. Cir. 2001). But here, the term "therapeutically effective" is in dispute because it is central to whether Goldwasser is properly considered prior art. *See In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (holding that a non-enabled disclosure will not suffice as § 102 prior art).

Although the endgame in the treatment of chronically anemic patients is to increase the hematocrit, as recognized by the district court, the claim term "therapeutically effective" must be understood in light of the specification of which it is a part. And that specification appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy. *See* '933 patent, col. 33, lines 19-31 ("[The claimed polypeptide products] are conspicuously suitable for use in erythropoietin therapy procedures . . . to develop any or all of the effects heretofore attributed in vivo to EPO, *e.g., stimulation of reticulocyte response . . ., erythrocyte mass changes . . ., and, as indicated in Example 10, increasing hematocrit levels in mammals*." (emphasis added)).

Amgen asserts that the district court's construction of "therapeutically effective" is supported by admissions of TKT's experts that the term means "increasing and maintaining the patient's hematocrit to normal or near normal levels." But the relevant question is not whether one of ordinary skill would so understand the term, but whether that term should be limited based upon the express disclosure in the specification. *CCS Fitness*, 288 F.3d at 1367, 62 USPQ2d at 1662-63 ("[A] claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the

invention."). If the claim term "therapeutically effective" encompasses the patient responses described in the specification, as it appears to us it does, then the Goldwasser study may constitute invalidating prior art under § 102(a) or § 103 even if he did not achieve his intended result. We therefore vacate the trial court's determination that Goldwasser cannot constitute prior art because the study was a failure. Resolution of the issue turns on the construction of the meaning of "therapeutically effective," which the trial court should have an opportunity to construe in the first instance under *Markman* principles. *See Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1349, 61 USPQ2d 1675, 1682 (Fed. Cir. 2002). Accordingly, on remand, the court should construe this term and, in light of that construction, should determine whether Goldwasser invalidates any of the asserted patents under 35 U.S.C. §§ 102(a) or 103.[20]

B

A second item of prior art germane to this appeal is United States Patent No. 4,377,513 ("Sugimoto"), issued in March 1983. Sugimoto discloses a process for producing human erythropoietin "characterized by multiplying human lymphoblastoid cells capable of producing human erythropoietin by transplanting said cells into a non-human warm-blooded animal body, or alternatively multiplying said cells by allowing said cells to multiply with a device by which the nutrient body fluid of a non-human warm-blooded animal is supplied to said cells, and allowing the cells multiplied by either of the above multiplication procedures to release

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[20] We note also that on remand when considering obviousness and anticipation issues relating to the '080 and '422 patents the district court should be cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations. *General Electric Co. v. Wabash Co.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884).

human erythropoietin." Sugimoto, col. 1, lines 30-38. Given the similarity of Sugimoto's disclosure to the patents asserted by Amgen, TKT naturally raised Sugimoto as potentially invalidating prior art, even though Sugimoto had been before the examiner.

The district court concluded that Sugimoto was not prior art under 35 U.S.C. § 102(a) because it was not proven to be enabled. *Amgen*, 126 F. Supp. 2d at 108, 57 USPQ2d at 1476 ("In light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race."). On appeal, TKT argues that the trial court erred in placing on it the burden of proving enablement of Sugimoto, because United States patents—even those only asserted as prior art in an invalidity defense—are presumed enabled under 35 U.S.C. § 282. We agree that prior art patents are presumed enabled, but under authority going beyond § 282.

A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to "enable one of skill in the art to reduce the disclosed invention to practice." *In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (C.C.P.A. 1962); *accord In re Donohue*, 766 F.2d at 533, 226 USPQ at 621. Thus, the critical issue here is not whether Sugimoto must be enabled, but rather whether it is the plaintiff or the defendant who bears the burden of proof with respect to that question.

On appeal, Amgen argues that there should be no presumption of enablement in this case because under § 282 courts only presume the claimed subject matter in a patent is enabled. Thus, Amgen argues, because only the unclaimed disclosures of Sugimoto are at issue here, no presumption of

enablement should apply. This argument is not relevant, however, because, as reasoned below, we do not only rely on § 282 as the source for a presumption. Instead, relying on our precedent, we hold a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.

In patent prosecution the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue.[21] *In re Sasse*, 629 F.2d 675, 681, 207 USPQ 107, 111 (C.C.P.A. 1980) ("[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a preponderance of the evidence." (citation omitted)). The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled. *Id.* We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. Thus, a court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled. Like the applicant in *ex parte* prosecution, however, the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and

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[21] Additionally, we think it unwise as a matter of policy to force district courts to conduct a mini-trial on the proper claim construction of a prior art patent every time an allegedly anticipating patent is challenged for lack of enablement. As we frequently revisit district courts' determinations in matters of claim construction and validity, we are certainly aware that such a task can occupy a great deal of a court's resources. In any event, because the presumption outlined here does not rely on § 282, we see no reason to impose these burdens on litigants and the district courts.

therefore are not pertinent prior art. If a patentee presents evidence of nonenablement that a trial court finds persuasive, the trial court must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption has been overcome.[22] Therefore, it was Amgen who bore the burden of proving the nonenablement of Sugimoto before the district court. TKT did not bear a bear burden of proving enablement.

Turning now to the district court's opinion, we think a fair reading is that the court, at least implicitly, put a burden of proving enablement of Sugimoto on TKT. The court began its analysis of Sugimoto by discussing evidence from Amgen and concluding "one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race [to make human EPO suitable for treating anemia]." *Amgen*, 126 F. Supp. 2d at 108, 57 USPQ2d at 1476. Proceeding from that standpoint, the court analyzed whether TKT's evidence was sufficient "to counter" this apparent conclusion that Sugimoto was not enabled. *Id.* at 108-09, 57 USPQ2d at 1476. Next, the court concluded its discussion of the enablement of Sugimoto by stating "TKT provided no evidence adequate to overcome the presumption that the Patent Office correctly rejected the contention that Sugimoto was an anticipating reference." *Id.* at 109, 57 USPQ2d at 1477. Importantly, only after apparently concluding that Sugimoto was not enabled did the district court discuss whether Sugimoto contained each and every limitation of any of Amgen's claims. The logical implication being that the court concluded that because TKT had not proven the enablement of Sugimoto, it could not anticipate any of Amgen's claims. In sum, we determine that ultimately,

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[22] We note that by logical extension, our reasoning here might also apply to prior art printed publications as well, but as Sugimoto is a patent we need not and do not so decide today.

the district court placed the burden of proving the enablement of Sugimoto on TKT.

In addition, looking at the evidence Amgen did present, we cannot conclude the district court properly found Amgen had met any burden that the court did place on it. At trial Amgen's expert, Dr. Erslev, testified that "no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure." *Id.* at 108, 57 USPQ2d at 1476. The mere fact that no one *has* so used the Sugimoto process is only minimally probative of nonenablement: a conclusion that no one *could have* used Sugimoto. Amgen also pointed out that Sugimoto was before the patent examiner during the prosecution of Amgen's patents. *Id.* While this was true, Sugimoto's non-enablement was only one of several arguments Amgen presented to overcome a rejection during prosecution and the examiner did not state his agreement with this position when he allowed the patent. Because we cannot assume the acceptance of every argument presented during prosecution, the mere fact this argument was made is also only minimally probative of the enablement of Sugimoto. In sum, the evidence presented by Amgen was insufficient to meet the burden Amgen apparently was assigned.

We must therefore conclude that to the extent it placed a burden on TKT the district court committed error. However, we hold this error to be, for the most part, harmless. After analyzing enablement and apparently finding the relevant unclaimed disclosures of Sugimoto nonenabled, the court nevertheless conducted a full anticipation analysis. Indeed, the district court performed a detailed analysis of each piece of anticipating prior art—including Sugimoto—asserted against each of Amgen's claims. *Id.* at 109-10, 57 USPQ2d at 1477. From this analysis the court found that "none of the cited references disclose [sic] each and every limitation of

any of Amgen's individual claims." *Id.* at 109, 57 USPQ2d at 1477. It does not appear that TKT has argued this alternative finding was clear error. However, we do not rest on waiver, but affirm the district court's finding that Sugimoto does not anticipate any asserted claims of the '080, '349, or '698 patents because from our review of the evidence and the subsidiary finding of the court, it was not clear error to find in each claim one or more limitations not disclosed in Sugimoto. But given our earlier holdings, we must vacate and remand the finding that Sugimoto does not anticipate claim 1 of the '422 patent. On remand, the district court should consider whether claim 1 of the '422 patent is novel over Sugimoto in light of the court's new definition of "therapeutically effective" and while mindful of the principle that source limitations cannot impart novelty to old compositions.

Our review is not yet finished, however, because it is apparent from the district court's opinion that TKT relied upon Sugimoto to assert invalidity of the patents in suit under both § 102 and § 103. In its obviousness inquiry, the district court disregarded Sugimoto because it concluded it was not enabled. It recognized, however, the important and potentially dispositive role that Sugimoto would have otherwise played in the obviousness analysis:

> Had the court concluded otherwise [*i.e.*, that Sugimoto was enabled], the Sugimoto patent would go a long way toward proving TKT's obviousness defense. As explained above, Sugimoto disclosed EPO-producing fused cells and advised that (1) conventional techniques can be utilized to achieve purification and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Thus, the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. Provided that one of ordinary skill in the art could actually make the EPO-producing cells described

> in the Sugimoto patent, a point on which TKT failed to persuade this court, such a combination of prior art materials might render invalid the pharmaceutical composition claims of the '933, '080, and '422 patents.

Id. at 114 n.29, 57 USPQ2d at 1480 n.29. Under § 103, however, a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein. See *Symbol Tech., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991); *Reading & Bates Constr. Co. v. Baker Energy*, 748 F.2d 645, 652, 223 USPQ 1168, 1173 (Fed. Cir. 1984). Therefore, the district court's obviousness holdings with respect to Sugimoto are vacated and remanded. On remand, the district court should reconsider obviousness with respect to Sugimoto, but should do so without reference to whether Sugimoto is enabled, as enablement of the prior art is not a requirement to prove invalidity under § 103.

V

The last issue on appeal is inequitable conduct. TKT raised before the district court essentially three instances of allegedly inequitable activities by the patentee: withholding crucial details regarding the Goldwasser study; withholding certain results of its own experiments that undermined the validity of the '933 patent; and failing to disclose to the Patent and Trademark Office the existence of this litigation. The district court found that TKT had not proven inequitable conduct by clear and convincing evidence, and we have not been persuaded on appeal that a contrary result is compelled. In reaching this conclusion, we need look no further than the district court's determination that TKT's case was doomed because it was bereft of evidence of intentional deception:

> TKT has failed to produce any persuasive evidence that causes the Court to doubt the integrity of the individuals who bore the duty of shepherding the Amgen patent applications through the Patent and Trademark Office,

> [so] its charge of inequitable conduct utterly fails . . . . TKT has failed to prove by clear and convincing evidence that this [experimental] data was material or that it was withheld with intent to deceive . . . . [And] TKT has not even begun to demonstrate that Amgen representatives possessed an intent to deceive the [PTO] in failing to provide specific notification regarding this litigation . . . . In summary, TKT's proof of inequitable conduct with respect to each of these charges falls short of the mark. Although the directness of Amgen's disclosures varies depending on the particular piece of disputed information, one truth remains the same throughout: Amgen's representatives never intended to deceive the Patent Office. Consequently, a finding of inequitable conduct would be error and the Court does not so find on the complete record.

Id. at 141, 145, 147, 57 USPQ2d at 1500, 1504, 1505.

A patent applicant commits inequitable conduct when, during prosecution of the application, he makes an affirmative representation of a material fact, fails to disclose material information, or submits false material information, and does so with the intent to deceive. *Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1581, 38 USPQ2d 1665, 1669 (Fed. Cir. 1996). As a general principle, materiality and intent are balanced—a lesser quantum of evidence of intent is necessary when the omission or misrepresentation is highly material, and vice versa *See, e.g., GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1273, 60 USPQ2d 1141, 1143 (Fed. Cir. 2001). At the same time, however, there must be some threshold showing of intent to be balanced; we will not find inequitable conduct on an evidentiary record that is completely devoid of evidence of the patentee's intent to deceive the PTO. *See Allen Eng'g Corp. v. Bartell Indus., Inc.*, No. 01-1238, 2002 U.S. App. LEXIS 15418, at *33 (Fed. Cir. Aug. 1, 2002) ("Materiality does not presume intent, which is a separate and essential component of inequitable conduct."

(quoting *Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567, 5 USPQ2d 1769, 1778 (Fed. Cir. 1988))).

Here, the district court determined that there was no evidence of intent to deceive, and TKT has directed us to none on appeal. Thus, to conclude the Amgen patents are unenforceable—as TKT requests—we must conclude (1) that the district court clearly erred by failing to find the minimal requisite intent to deceive, and (2) that it abused its discretion in weighing the degree of materiality against the degree of deceptive intent and by not then rendering the patents unenforceable. On the record before us, we decline to do so.

CONCLUSION

We summarize our decision as follows. Affirmed are: the district court's claim construction; its finding that all of the patents in suit are enforceable; its finding that the '933 patent is invalid; and its finding that the '349 (product claims only) and the '422 patents are infringed. We vacate: its finding that the '933 patent was not infringed; several of its validity findings with respect to the '080, the '349, the '422, and the '698 patents; and its infringement findings with respect to the '698 patent and '349 patent claim 7. On remand, the district court should: construe the claim term "therapeutically effective" and then reconsider validity under §§ 102 and 103 in view of Goldwasser; reconsider validity of all asserted claims under § 103 and claim 1 of the '422 patent under § 102 in view of Sugimoto, with Amgen bearing the burden of proof on its non-enablement (for § 102 purposes only); reassess infringement of the accused method by comparing it solely to the limitations of each of the asserted method claims; and reevaluate its finding of infringement under the doctrine of equivalents of the '080 patent, focusing on the application of prosecution history estoppel.

AFFIRMED IN PART, VACATED IN PART, REMANDED. No costs.

CLEVENGER, *Circuit Judge,* dissenting in part.

I join my colleagues' thorough opinion in all respects save one, albeit significant, exception. Because the claims lack meaningful limitations on the structure of the erythropoietin-producing cells, I cannot agree that the district court should have abstained from inquiring fully whether the claims were suspect under the enablement and written description provisions of 35 U.S.C. § 112, ¶ 1.

As described by the specifications of the patents in suit, Amgen in 1984 cloned and sequenced the DNA encoding human erythropoietin (EPO). Amgen then showed that by introducing the cloned EPO DNA (linked to a promoter sequence) into mammalian cells, those cells could be engineered to express high levels of functional human EPO protein. The parties refer to this as "exogenous DNA" expression of EPO. Amgen obtained several patents that cover the use and manipulation of cloned EPO DNA, and these patents, battle-tested through litigation, have been the foundation of Amgen's successful business of manufacturing and selling recombinant EPO. But these patents are not in suit here, and TKT's method for producing EPO does not rely upon manipulation of cloned EPO DNA or "exogenous DNA" expression technology.

The claims in suit here contain no significant limitations as to how the recombinant EPO is expressed, or as to the structure of the EPO-producing cells, so long as the EPO is "non-naturally occurring" or produced in "vertebrate cells." The central question in this case is therefore whether Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultured vertebrate cells that produce EPO. I think this is a question of some importance. Yet it is a question that the district court simply refused to consider. Although the district court admitted that Amgen's disclosure

was limited to exogenous DNA expression, the district court quite clearly and explicitly refused to decide whether the absence of any exogenous DNA limitations rendered the asserted claims vulnerable to the enablement challenge mounted by TKT under section 112. According to the district court, because the asserted claims were to "compositions" rather than "processes," "the specification need teach only one mode of making and using a claimed composition." *Amgen Inc. v Hoescht Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 160, 57 USPQ2d 1449, 1515 (D. Mass. 2001). *See also id.* at 160, 164 n.57, 57 USPQ2d at 1516, 1518 n.57. Likewise, the district court refused to inquire whether the absence of limitations on the means of EPO expression raised questions of compliance with the written description requirement, holding that such an inquiry was irrelevant to composition claims. *Id.* at 150-51, 57 USPQ2d at 1508.

With respect to the '080 and '422 patents, which claim "non-naturally occurring" EPO and EPO "purified from mammalian cells grown in culture," the majority, like the district court, essentially passes over the question of whether these limitations—which are essential for patentability of the claims—raise issues of compliance with the enablement and written description requirements of section 112. The majority holds that patentees are free to decorate their composition claims with source and process limitations without any concern for whether the full scope of those limitations is enabled or described, and that these requirements of section 112 are waived so long as the patentee succeeds in characterizing its claims as "product" claims. Competent patent attorneys should be quick to take advantage of the majority's broad exemption from the disclosure requirements by the appropriate phraseology. Rather than endorse the district court's elevation of form over substance, I would vacate its decision on these issues regarding the '080 and '422 patents, and remand for further consideration in light of the vast scope of

the claims in suit for which there appears to be insufficient enabling disclosure or written description.

With particular reference to the '349 patent, which claims not EPO polypeptides but the cells that produce them, I think the district court's abstention from scrutiny under section 112 is even more patent error. The majority focuses on the district court's findings that the invention could readily be practiced in mammalian or vertebrate cells other than the hamster and monkey cells taught by the specification. I agree that TKT has not shown error in these findings. But, as it did for the EPO claims, the district court simply refused to consider whether the absence of any exogenous DNA limitations raised enablement issues, "[b]ecause Amgen is only required to enable skilled artisans to make its claimed product by only one method . . . ." *Id.* at 164 n.57, 57 USPQ2d at 1518 n.57. For the EPO-secreting cells, the absence of an exogenous DNA limitation is not a failure to limit how the product is made, but a failure to limit the structure of the claimed product itself. A cell, as employed in the patents in suit, is nothing more than a biological machine for making EPO. Even in more predictable arts, one who is first to make a machine is not entitled as a matter of law to claim any or all machines so long as they perform the same function. I would think it uncontroversial that even one who is first to make polymer X or alloy Y cannot obtain a claim as broad as "A machine that makes polymer X," or "A process that yields alloy Y," without reciting additional limitations that define the structure of the claimed machine or the steps necessary to carry out the claimed process.

Yet that is exactly what the district court and the majority allow the '349 patent to achieve. It claims any or all cultured vertebrate cells that can secrete a defined amount of EPO, with only a single limitation on their structure: that they "compris[e] non-human DNA sequences which control transcription of DNA encoding human erythropoietin," or that

they "comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin." This is little more precise than a recitation of "A machine that makes polymer X, wherein the machine comprises means for controlling how much polymer X is made." The specification teaches only a single means by which the use of a transcription control sequence can coax a vertebrate cell to secrete EPO: by transforming that cell with an exogenous expression vector on which the transcription control sequence is linked to cloned EPO DNA. Yet the claims leave this essential aspect of the invention undefined. It is black-letter law that claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure, *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976), and that disclosure of one or two species may not enable a broad genus under these circumstances. *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). At the very least, the absence of structural limitations in the '349 patent raises questions of its enablement, and I cannot agree that the district court chose correctly by ignoring those questions altogether. We should vacate the district court's judgment that the '349 patent passes enablement muster, and require the court to apply the correct law to the plain facts.

I must also disagree with the majority that the district court's approach was faithful to this court's articulation of the written description requirement of section 112, as expressed in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998). *Eli Lilly* articulated two principles of the written description requirement: that *in haec verba* description of broadly described generic subject matter may not suffice to describe the subject matter of that particular claim, 119 F.3d at 1567, 43 USPQ2d at 1404-05, and that disclosure of a species may not suffice to describe a genus, *id.*

at 1568-69, 43 USPQ2d at 1405-06. The district court followed neither of these principles here, and the majority, dismissing *Eli Lilly* on the grounds that no undisclosed DNA molecule appears in this case, verges on confining *Eli Lilly* to its facts.

Nor am I convinced that the district court's approach was faithful to *Gentry Gallery*. In *Gentry*, only those claims that included limitations such as "wherein the control means are located on the console" satisfied the written description requirement. Because the specification failed to disclose any location for the controls other than on the console, those claims that lacked such limitations were invalid under § 112, ¶ 1. 134 F.3d at 1479-80, 45 USPQ2d at 1503-04. The question here is similar: whether the claims fail the written description requirement for lack of "exogenous DNA" limitations, because the specification discloses only the exogenous DNA technology that was state of the art in 1984.

Even if we ignore the patents' statement that the claimed EPO molecules are "uniquely characterized by being the product of . . . expression . . . of exogenous DNA sequences" (which of course we cannot), I think the parallels between this case and *Gentry Gallery* are inescapable. The invalid claims in *Gentry* recited elements that could readily be found in the text of the specification (a couch, controls, a console), but those claims nonetheless failed the written description requirement because they included no limitations on how those elements were *arranged*. Likewise, the '349 claims—for which I think it must be conceded that structure of the EPO-secreting cell is a relevant question—recite particular elements found in the specification (cells, non-human control sequences, EPO-coding DNA), but do not include limitations on the arrangement of those elements, *e.g.* that the non-human control sequences and coding DNA are present on an exogenous expression vector in the cell. I agree that as a matter of claim interpretation there is no justification for

importing an "exogenous DNA" limitation into the claims. But the absence of such limitations must weigh heavily in the section 112 inquiry, else we hold that claims become more resistant to written description challenges the more broadly drafted they are.

While I share my colleagues' admiration for the considerable efforts of the district court in this complicated case, I cannot share their faith that the district court properly and conscientiously applied *Eli Lilly* and *Gentry Gallery*, when the district court's opinion is completely devoid of reference either to those cases or to the principles they espouse. If the district court did not focus on the correct law to be applied, then its factual findings merit no deference, and the correct remedy for this omission is to vacate the district court's judgment on this point and remand for further consideration. Our precedent has little value if the district courts may overlook its certain pertinence, if not its plain applicability.

APPENDIX E

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 97-10814-WGY

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC. and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

FINDINGS, RULINGS, AND ORDER

YOUNG, C.J. January 19, 2001

In this jury waived declaratory judgment action, Amgen, Inc. ("Amgen") seeks a declaration that certain of the patents protecting its best selling drug EPOGEN® are infringed by the conduct of the defendants, Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (collectively "TKT"). TKT denies infringement and, in turn, counterclaims that Amgen's patents are invalid on a number of grounds.

Amgen, the first to discover and manufacture a recombinant DNA product similar to natural erythropoietin ("EPO") and useful in various medical treatments, has reaped significant commercial rewards from its discoveries, *see* Patricia Van Arnum, *Active Pharmaceutical Ingredients: The Opportunities in the Branded Prescription Market*, Chemical Market Rep., Oct. 30, 2000, WL 10/30/00 CHEMMKT REP FR 14 (noting that Amgen's Epogen had sales of $1.76 billion in 1999); Vicki Brower, *Amgen Comes Out on Top in Blood Drug Patent Tussle*, Biotechnology Newswatch, Jan. 4, 1999, WL 1/4/99 BIOTECHNW 1 (noting that EPO was then

the "biggest-selling biotechnology drug ever developed" and that Amgen's EPO sales accounted for over fifty percent of its 1997 $2.4 billion revenue). As one would expect, Amgen has sought to preserve its commercial success through a cluster of related patents that it has defended with skill and perseverance.[1]

In conjunction with Hoechst Marion Roussel, Inc., now known as Aventis Pharmaceuticals, Inc., TKT, a smaller company, seeks to capitalize upon apparent advances in genetic engineering by targeting the most lucrative commercial recombinant DNA products and designing around them. *See* Trial Tr. at 1772:21 to 1773:2, 1786:5 to 1787:7. It, too, as one might expect, is no stranger to litigation.[2] The present

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[1] *See, e.g., Amgen, Inc.* v. *Elanex Pharm., Inc.*, No. C93-1483D, 1996 WL 84590 (W.D. Wash. Feb. 6, 1996); *Amgen, Inc.* v. *Genetics Inst., Inc.*, 877 F. Supp. 45 (D. Mass. 1995), *aff'd*, 98 F.3d 1328 (Fed. Cir. 1996); *Amgen, Inc.* v. *Chugai Pharm. C., Ltd.*, No. 87-2617-Y, 1989 WL 169006 (D. Mass. Dec. 11, 1989), *aff'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1989), *cert. denied*, 502 U.S. 856 (1991); *Ortho Pharm. Corp.* v. *Amgen, Inc.*, 709 F. Supp. 504 (D. Del.), *vacated in part*, 882 F.2d 806 (3d Cir.), *appeal after remand*, 887 F.2d 460 (3d Cir. 1989); *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 706 F. Supp. 94 (D. Mass. 1989); *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1731 (Bd. Pat. App. & Interf. 1991); *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1737 (Bd. Pat. App. & Interf. 1991); *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1739 (Bd. Pat. App. & Interf. 1991); *In the Matter of Certain Recombinant Erythropoietin*, 10 U.S.P.Q.2d (BNA) 1906 (U.S. Intl Trade Comm'n 1989), *vacated*, *Amgen, Inc.* v. *United States Intl. Trade Comm'n*, 902 F.2d 1532 (Fed. Cir. 1990).

[2] *See Amgen, Inc.* v. *Hoechst Marion Roussel*, 190 F.R.D. 287 (D. Mass.), *aff'd*, 232 F.3d 905, 2000 WL 290346 (Fed. Cir. 2000) (un-published decision); *Aetna U.S. Healthcare, Inc.* v. *Hoechst Aktiengesellschaft*, 54 F. Supp.2d 1042, *reconsid. denied*, 67 F. Supp. 2d 1242 (D. Kan. 1999); *Biovil Corp. Int'l* v. *Hoechst Aktiengesellschaft*, 49 F. Supp. 2d 750 (D.N.J. 1999); *Aetna U.S. Healthcare, Inc.* v. *Hoechst Aktiengesellschaft*, 48 F. Supp. 2d 37 (D.D.C. 1999); *Eli Lilly & Co.* v. *Roussel Corp.*, 23 F. Supp. 2d 460 (D.N.J. 1998); *Mut. Pharm. Vo., Inc.* v. *Hoechst Marion Roussel, Inc.*, 46 U.S.P.Q.2d (BNA.) 1148 (E.D Pa. 1997); *Hoechst Marion Roussel, Inc.* v. *Scherinq-Plough Corp.*, No. 97-

litigation, in fact, has been brewing for some time, *see Amgen, Inc* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D. Mass. 1998), and when it ultimately erupted in June of 1999, the parties were ready.

As an aside, it is only just to note that this case has been presented with high integrity, an unswerving fidelity to court rules and procedures, and a consummate excellence in trial practice that makes it a model not only for the intellectual property bar, but for lawyers everywhere. Any failings in understanding are mine, and mine alone.

The course of the litigation may be briefly sketched.

Early on, the parties agreed on a list of experts upon whom the Court might call for technical assistance. The Court chose Professor Chris Kaiser of the Massachusetts Institute of Technology from this list, and has met privately with him for background tutorial assistance.[3]

0147-CV-W-5, 1997 WL 79796 (W.D. Mo. Feb. 10, 1997); *Hoechst Marion Roussel, Inc.* v. *Par Pharm. Inc.*, 39 U.S.P.Q.2d (BNA) 1363 (D.N.J. 1996).

[3] While not in any way original to this Court, the use of and protocol followed by the Court with technical advisors is extensively discussed in *MediaCom Corp.* v. *Rates Tech., Inc.*, 4 F. Supp. 2d 17, 29-30 (D. Mass. 1998) (tracing Judge Richard Stearns' technique of using technical advisors in *Biogen, Inc.* v. *Amgen, Inc.*, No. 95-10496-RGS [D. Mass. Dec. 10, 1996]). As this Court remarked in *MediaCom*, the technique employed by Judge Stearns is extraordinarily helpful to any judge faced by complex technical litigation. Not surprisingly, the use of technical advisors has received favorable comment locally, *see* Richard Stearns' Remarks at the Massachusetts Continuing Legal Education's Federal Judicial Forum (Oct. 16, 2000) (attributing the original idea to Judge Charles Wyzanski in *United States* v. *United Shoe Machinery Co.*, 223 F. Supp. 826 [D. Mass. 1963]), nationally, *see* Sandy Choi, *A Perspective on Patent Claim Construction After* Markman v. Westview, in *Federal Courts, Judicial Forum 2000,* at 392 (William G. Young ed. 2000), and even internationally, *see* Shinichi Yoshikawa & Aya Takahashi, *The Use of Experts in the Pre-trial Stage of Civil Litigation that Concerns*

Towards the close of discovery, Amgen moved for summary judgment on the issue of infringement.[4] This motion necessitated construction of the patent claims, and the Court held a *Markman* hearing on March 27, March 28, and April 10, 2000. Thereafter, the Court granted summary judgment to Amgen on a particular claim in one of the five patents in issue. The motion for summary judgment was otherwise denied.

Trial commenced on May 15, 2000 and continued for twenty-three days spread over four months.[5] At the close of Amgen's case in chief, the Court held, pursuant to Fed. R. Civ. P. 52(c), that TKT had not infringed the process claims of Amgen's U.S. Patent No. 5,618,698 (issued Apr. 8, 1997). Trial concluded on September 8, 2000, and the matter was taken under advisement.

Technical Issues—Technical Advisors in Markman *Hearings in Patent Litigation in the United States*, 104 Law J. Legal Training & Res. Inst. 67 (2000). Under an imaginative program sponsored by the Supreme Court of Japan, Judge Yoshikawa of the Osaka District Court and Judge Takahashi of the Tokyo District Court actually sat with this Court during the trial and post-trial consideration of this case.

In one respect, the Court refined the protocol discussed in *MediaCom*. In this case, every contact with Professor Kaiser has been made a matter of record. While this record remains sealed, it is, of course, available to any appellate court should it so require.

[4] A motion for summary judgment is, of course, an excellent vehicle to frame the essential questions of patent claim construction. *See MediaCom*, 4 F. Supp. 2d at 22-23. Moreover, the timing of the *Markman* hearing in this case was optimal. *See MacNeill Eng'g Co.* v. *Trisport, Ltd.*, No. 98-12019, slip op. at 7 (D. Mass. Jan. 10, 2001).

[5] One curious aspect of this case illustrates perfectly the utterly speculative nature of the stock market during the Spring and Summer of 2000. Each day of trial, the courtroom would fill with the financial press, financial analysts and their hangers-on, and lawyer commentators. Each day at the morning break (10:45 a.m.) and the luncheon recess (1:00 p.m.), this group would debark into the hallway, activate their cell phones,

I. THE PATENTS AT ISSUE

There are five patents at issue in this case: U.S. Patent No. 5,547,933 (issued Aug. 20, 1996) ("'933 patent"), Trial Ex. 2; U.S. Patent No. 5,618,698 (issued Apr. 8, 1997) ("'698 patent"), Trial Ex. 4; U.S. Patent No. 5,621,080 (issued Apr. 15, 1997) ("'080 patent"), Trial Ex. 3; U.S. Patent No. 5,756,349 (issued May 26, 1998) ("'349 patent"), Trial Ex. 5;

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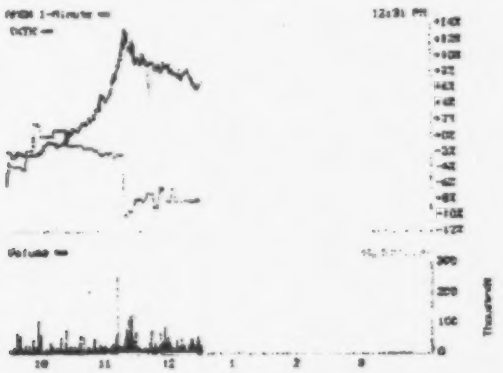
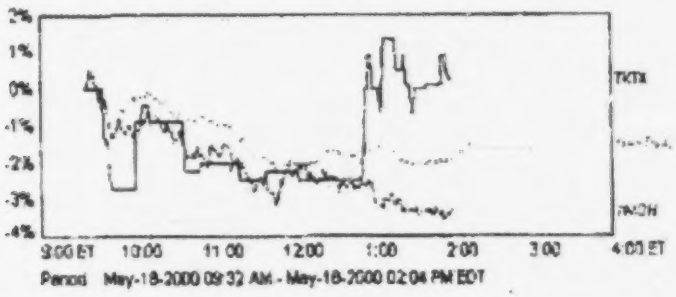
and shortly thereafter the publicly-traded stocks of the litigants would bob or dip in response to some random comment by the Court, the trial lawyers, or a particular witness. The two charts below, from April 26 and May 18, 2000 respectively, illustrate the speculative phenomenon.



Interactive Charting for Amgen, Inc., *at* http://www.marketwatch.com (last visited Apr. 26, 2000).



[S] = stock split or spinoff

Amgen's MASDAQ Quote, *at* http://www.quicken.com (last visited May 18, 2000).

and U.S Patent No. 5,955,422 (issued Sept. 21, 1999) ("'422 patent"), Trial Ex. 6.

All of these patents share a common disclosure and identical specifications. Trial Exs. 2-6. Only the claims differ. Each of the patents claim priority from the following common applications: U.S. Patent Application Serial No. 675,298 (Nov. 30, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 655,841 (Sept. 28, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 582,185 (Feb. 21, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 561,024 (Dec. 13, 1983). Trial Exs. 2-6.

II. "THE NAME OF THE GAME IS THE CLAIM":[6] CLAIM CONSTRUCTION

It is appropriate to pause for a moment to emphasize the particular procedural approach that this Court used in conducting the *Markman* hearing. District courts have differed significantly in the timing and procedure for *Markman* hearings—some engaging in claim construction prior to trial and others after hearing all of the evidence at trial. *See* William F. Lee & Anita K. Krug, *Still Adjusting to Markman: A Prescription for the Timing of Claim Construction Hearings*, 13 Harv. J.L. & Tech. 55, 73 (1999). I have consistently taken the procedural approach of conducting the *Markman* hearing at the summary judgment stage of litigation or at the point when discovery has closed and trial is approaching. *See, e.g.*, *MacNeill Eng'g Co.* v. *Trisport, Ltd.*, No. 98-12019, slip op.

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[6] Giles S. Rich, *Extent of Protection and Interpretation of Claims—American Perspectives*, 21 Int'l Rev. Indus. Prop. & Copyright L. 497, 499 (1990); *see* T. Whitley Chandler, *Prosecution History Estoppel, the Doctrine of Equivalents, and the Scope of Patents*, 13 Harv. J.L. & Tech. 465, 479 (2000) ("Every patent decision today first pays homage to the exalted status of the *claims*. Why? Because the right to exclude does not turn on what was invented, but what is *claimed*.") (footnote omitted).

at 7 (D. Mass. Jan. 10, 2001); *MediaCom*, 4 F. Supp. 2d at 22-23. I have taken care to note that the benefits of so doing range from constitutional concerns arising from conducting such a hearing too soon to efficiency concerns arising from conducting the hearing too late. *See MediaCom*, 4 F. Supp. 2d at 22; Lee & Krug, *supra* at 82-85.

Here, however, I want more specifically to emphasize that when the *Markman* hearing is conducted at the summary judgment stage, it is also important to conduct the two hearings independently of each other—the *Markman* hearing being held prior to and entirely independently of the summary judgment hearing. This is exactly the procedure that the Court followed in the case at hand, although other courts have chosen to address the issues raised with respect to claim construction in the context of the motion for summary judgment and hence conduct the *Markman* hearing in conjunction with the hearings on summary judgment, *see, e.g.*, *Biogen* v. *Berlex Labs., Inc.*, 113 F. Supp. 2d 77, 81 (D. Mass. 2000) (conducting the *Markman* hearing "in connection with" the summary judgment hearings).

This Court's *Markman* procedure turns on what this Court sees as the crucial distinction between construing patent claims in the *context* of considering motions for summary judgment as opposed to construing the patent claims *without regard* to the alleged infringement issue presented in the summary judgment motion. With this distinction in mind, this Court scrupulously kept the issues separate in order to avoid conflating the legal explication required by *Markman* with the fact finding that the Seventh Amendment ultimately reserves for the American jury. *See Ciulla* v. *Rigny*, 89 F. Supp. 2d 97, 101, 102 & n.7 (D. Mass. 2000) (discussing the constitutional and communitarian values strengthened by jury fact finding)

Although, under current law, both approaches are permitted in the wake of *Markman*, just as the Federal Circuit has spoken to the question of what evidence a court should

consider in a *Markman* hearing, *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582-83 (Fed. Cir. 1996), perhaps it ought similarly fashion flexible procedural boundaries within which to conduct such a hearing. Failure to do so not only deprives litigants of the benefit of consistent treatment among districts (or even among specific judges), but also risks descending a slippery slope toward the erosion of the role of the fact finder in patent litigation.

This latter fear is the central concern of this Court with the procedural approach to *Markman* hearings that mixes issues of claim construction with that of infringement by simultaneously considering factual evidence of each. I concede that, analytically, such mixing ought not affect the outcome of claim construction. Nonetheless, I fear that such mixing cuts against the spirit of both *Markman* itself and its recognition of the importance of the fundamental divide between fact and law (and consequently, fact finder and law definer) upon which our legal system is based because it openly invites the risk that issues of fact and law will be conflated.[7] Indeed, to limit procedurally the consideration of factual issues at the *Markman* hearing is analogous to the Federal Circuit's own warning against the consideration of extrinsic evidence where intrinsic evidence alone will adequately allow for definition of the disputed claim term. *See Vitronics Corp.*, 90 F.3d at 1583.

Judges are expected to be objective and analytic in their role as law definer, and I daily seek to meet this standard. Moreover, I do not even mean to suggest that the outcome of this case would have somehow been different had this Court followed the approach that other courts apply and mixed the

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[7] Of course, mixing the *Markman* hearing with the court's consideration of summary judgment merely creates such a risk. Careful parsing of the issues can avoid this risk of conflating fact and law. *See Biogen*, 113 F. Supp. 2d at 101 (court stated explicitly in its claim construction that it did not rely on extrinsic evidence of invalidity in construing the claims).

questions of claim construction into the hearing on summary judgment. But the risk that this procedure creates of conflating issues of fact and law is simply too high in my eyes. Let us not forget that the Seventh Amendment requires that infringement cases be tried to a jury. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). The judiciary has recently mandated other procedural hurdles that seem to fly in the face of efficiency in the sole effort to preserve the role of the American jury. *See Apprendi* v. *New Jersey*, 530 U.S. 466 (2000). Believing in the benefits of such a simple prophylactic measure—considering claim construction without regard to infringement—I made careful efforts to follow this procedure consistently. The result is an honest effort to give meaning to the true spirit of *Markman* and the due consideration that it gave to the role of the jury in patent litigation.

During the three-day *Markman* hearing, the Court entertained oral argument from counsel for each party with respect to ten claim terms that were pre-selected due to their relationship to disputed issues arising in Amgen's pending summary judgment motion. Counsel referred the Court to relevant portions of the specification as well as the prosecution history. Demonstrative exhibits were utilized, but evidence was neither offered nor admitted. After hearing each party's presentation, the Court announced its constructions.

During the course of the *Markman* hearing, the positions of each party remained generally consistent. On the one hand, Amgen consistently advocated what the Court referred to as the "ordinary meaning" of a particular claim term. On the other hand, TKT often sought to insert a limitation by arguing that without such limitation, the claim would be invalid for lack of adequate description or enablement. Their positions, of course, were not surprising. As the patent holder, Amgen had every incentive to persuade the Court to adopt the broadest possible interpretation in order to sweep within its

patents' span the greatest possible amount of its competitors' activities. TKT meanwhile proffered limiting interpretations with an eye toward distinguishing its products and process from the scope of the patents' language. This dance is well known.[8] Both parties cite Federal Circuit case law that appears to support their conflicting views, thus creating the impression that the case law itself is contradictory. A close examination of this case law, however, reveals that TKT's approach—though accepted in some limited circumstances—is inappropriate here.

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[8] These well known strategies for claim construction have, in fact, reached the point of ridicule in the patent subculture as this inciteful poem (to be sung to the tune of "Camelot") exemplifies:

A law was made 200 years ago here
Grant patents, help promote inventive thought
Today the system's thriving and our credo
Is claim-a-lot

We push the envelope,
expand the boundaries
Create a circle from a tiny dot
Our product's forged with words
and not in foundries
We claim a lot

(Bum bum, etc.)

Claim-a-lot (claim-a-lot)
I know it sounds a bit bizarre
Lord, we claim-a-lot (oh yes, we claim-a-lot)
Stretch out those claims so far

Though prior art may set some limitations
Restricts our flights of fancy, clever thought
Our efforts, not for naught
Results, so boldly wrought
Construct our patent juggernauts
By claiming quite a lot.

Kramer, Levin, Naftalis & Frankel LLP, *Claim-a-Lot*, *in* Pamphlet for N.Y. Intellectual Property Law Association 78th Annual Dinner (Mar. 24, 2000).

In many instances, Amgen relied primarily on the familiar notion that "[f]irst, and most importantly, the language of the claim defines the scope of the protected invention." *Bell Communications Research, Inc.* v. *Vatalink Communications Corp.*, 55 F.3d 615, 619 (Fed. Cir. 1995); *see also Renishaw Plc* v. *Marposs Societa' Per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("[T]he claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim. [T]he resulting claim interpretation must, in the end, accord with the words chosen by the patentee to stake out the boundary of the claimed property."); *Abtox, Inc.* v. *Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997) ("[T]he language of the claim frames and ultimately resolves all issues of claim interpretation."). Relatedly, absent a clear and specific statement in the patent specification giving a claim term a special definition, the Court must adopt the plain and ordinary meaning given by persons experienced in the field of the invention. *See Renishaw*, 158 F.3d at 1249; *Hoechst Celanese Corp.* v. *BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996); *see also Digital Biometrics, Inc.* v. *Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) (patentee may be her own lexicographer). Adhering to these cardinal principles of claim construction, this Court discharges its duty of claim construction by interpreting the claim terms pursuant to the plain and ordinary meaning ascribed to them by one skilled in the art.

Derived from these core principles is the additional canon of claim construction that a court may not read a limitation into a claim from the written description, but may look to the written description to define a term already in a claim limitation, for a claim must be read in light of the specification. *Vitronics Corp.*, 90 F.3d at 1582. Thus, even when the Court looks at intrinsic evidence to assist it in identifying the meaning of a claim term, the words of the claim should still be given their preeminence. This canon creates a fine but important line for the Court to walk: "It is entirely proper to use the specification to interpret what the patentee meant by a

word or a phrase in the claim. But this is not to be confused with adding an extraneous limitation appearing in the specification, which is improper." *E.I. du Pont De Nemours & Co.* v. *Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) (citation omitted); *see generally* David C. Radulescu, *The Federal Circuit's Narrowing of the Literal Scope of Patent Claims by Focusing on Embodiments Disclosed in the Specification*, 82 J. Pat. & Trademark Off. Soc'y 59 (2000). To ensure that a litigant does not improperly cross this line, a party wishing to use statements in the written description to confine a patent's scope must first point to a term in the claim with which to incorporate those statements. *Renishaw*, 158 F.3d at 1248. "Without any [such] claim term that is susceptible of clarification by the written description, there is no legitimate way to narrow the property right." *Id.* Under such circumstances, use of the specifications to "define" the claim term would impermissibly cross over the line by using the specifications to add extraneous limits on the patent.[9]

In contrast, TKT relies most heavily upon a number of Federal Circuit cases standing for the proposition that claims ought be construed so as to sustain their validity. *See, e.g.*, *Wang Labs.* v. *Am. Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999). During the claim construction phase of the case,

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[9] The line between interpreting claim language in light of the specification and adding an extraneous limitation from the specification is relevant in other canons of construction. As will be seen, the doctrine upon which TKT relied that claims ought be construed so as to sustain their validity should be subject to the same restriction. Thus, although the Federal Circuit has stated that "if the claim is susceptible to a broader and a narrower meaning, and the narrower one is clearly supported by the intrinsic evidence while the broader one raises questions of enablement under § 112, ¶ 1, we will adopt the narrower of the two," *Digital Biometrics*, 149 F.3d at 1344, this is nonetheless subject to the limitation that the party seeking to incorporate a limitation by relying on the specification must first identify a claim term hook susceptible of the narrower meaning upon which to hang the limitation.

counsel for TKT implored the Court to reject Amgen's proffered interpretations because such broad interpretations were not adequately disclosed in the patents' specification. In short, TKT argued that while Amgen taught the production of EPO using a precise process and specific cells, Amgen went on to claim far beyond its teachings. Thus, if the Court adopted a claim construction commensurate with the plain and ordinary meaning of the overbroad claim terms, its construction would run counter to the Federal Circuit's command that claims be construed so as to sustain their validity..

Indeed, incorporating validity concerns during claim construction may apply "where there are several common meanings for a claim term" and thus "the patent disclosure serves to point away from the improper meanings and toward the proper meaning." *Renishaw*, 158 F.3d at 1250. In this sense, the canon that claim terms ought be construed to sustain their validity is simply an interpretation tool to aid courts in determining what a reasonably disputed claim term means in light of the specifications. The Federal Circuit has warned, however, that the canon that claims ought be interpreted to sustain their validity is not without limits:

> The [Supreme] Court has consistently limited the axiom [that claims should be interpreted to preserve their validity] to cases where the construction is "practicable" and does not conflict with the explicit language of the claim. [The Federal Circuit also has] consistently employed the caveat, "if possible," to our instruction that claims should be construed to sustain their validity. We have also admonished against judicial rewriting of claims to preserve validity . . . .

Rhine v. *Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) (citations omitted). With this limitation in mind, the claim term being construed must first be reasonably capable of the interpretation that is purportedly favored by the arguments for invalidity. Thus, in employing this doctrine, the Court is not

permitted to construe a term that has a plain and ordinary meaning in a manner contrary to that meaning. This, of course, would constitute the type of "judicial rewriting" about which the Federal Circuit has warned. *See id.* Nor does it grant courts the authority to somehow jump to the conclusion that a claim term is reasonably susceptible of competing interpretations. Simply put, the doctrine does not grant courts the power to employ validity arguments to limit claim terms where such claim terms, even considering all alternative definitions, could not reasonably be construed to incorporate such limits. In such circumstances, validity concerns must lie in the province of the fact finder.

There is good reason, of course, to avoid conflating invalidity concerns with claim construction. First, the Court is mindful that determining whether a patent is invalid because it lacks a sufficient written description is an issue of fact. *See Union Oil Co. of Cal.* v. *Atl. Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000). As a result, in a jury case, the members of the jury should determine whether the patent adequately describes each element of the claimed invention. If the Court were to conflate invalidity concerns involving the written description requirement with claim construction, then a function reserved for the jury would be usurped by the trial judge. At the same time, the Supreme Court has made clear that construing the claims of a patent is an issue of law and, as such, claim construction is within the province of the trial judge. *See Markman*, 517 U.S. at 386. The conflict, then, becomes clear. If the Court were to select a construction that it believed was more consistent with the written description of the patent but contorted the language of the claim terms in order to do so, the jury, in effect, would be preempted from making the invalidity determination, which is within its province. This the Court cannot do.

Second, one must be cognizant that Congress has determined that "[a] patent shall be presumed valid." 35 U.S.C.

§ 282. This congressionally-mandated presumption of validity not only places the burden of proving invalidity on the defendant, but also requires the defendant to prove the point by clear and convincing evidence. *Sibia Neurosciences, Inc.* v. *Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). In order to give congressional will the deference it deserves, courts ought not permit defendants to shirk this responsibility by arguing that concerns regarding validity should be accounted for during claim construction. Instead, it strikes the Court that the proper way to proceed, where it is possible, is to interpret the claim terms consistent with their plain and ordinary meaning and hold the defendant to its burden to prove invalidity by clear and convincing evidence. Any other approach would neglect the congressional mandate.

In this case, the Court ruled during the *Markman* hearing that TKT's claim construction theory extends the canon that claims ought be construed in favor of their validity far beyond its intended reach. Instead, as explained below, because the terms to be construed simply are not reasonably capable of the interpretation proffered by TKT, it became apparent that TKT was actually attempting to add limitations to claim terms rather than merely attempting to define the disputed terms. At the end of the day, the canon that claims ought be construed so as to sustain their validity simply does not include under its umbrella TKT's arguments as they apply in this matter.

With these concerns in mind, the Court conducted the *Markman* hearing and interpreted ten words and phrases central to the patents-in-suit and the dispute between the parties. Each term, the arguments relevant to it, and the Court's construction are reproduced below seriatim.[10]

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[10] It should be noted that while the focus of the *Markman* hearing was on the patents themselves, the Court writes now with the benefit of having presided over the entire trial.

A. *Vertebrate Cells*

The term "vertebrate cells" is contained in Claims 4, 6, and dependent Claim 7 of the '698 patent and Claims 1, 4, and dependent Claims 3, 6, and 7 of the '349 patent. There is no contention by either party that the term should have a different meaning in the various claims. Aside from that agreement, however, the parties (not surprisingly) proffered quite different constructions. Amgen contended that "vertebrate cells" means "cells originating from an animal having a backbone," Pl.'s *Markman* Hr'g (Mar. 27, 2000) Demonstrative Ex. 12, whereas TKT argued that the term means "non-human cells that originate from an animal having a backbone," Defs.' *Markman* Hr'g Demonstrative Ex. 1. Thus, while Amgen proffered the broad, albeit ordinary meaning of the term, TKT sought to have the Court add a limitation to the claim by including the word "non-human."

The reason for the particular distinction between the parties' proffered constructions is, not surprisingly, fueled by the related infringement and validity analysis. In order to make EPO, TKT activates the native human EPO gene in a human cell. As a result, there is little wonder why TKT offered, and Amgen vehemently opposed, a construction of the term "vertebrate" that excluded human cells. Had the Court adopted TKT's version, it would have been bound to issue, upon proper motion, summary judgment of non-infringement—at least as to literal infringement. That, of course, is no reason to reject TKT's proffer, but merely explains the importance of construing the term appropriately.

While counsel for TKT admitted that its construction was contrary to the ordinary meaning of the term "vertebrate," TKT argued that "the terms of a claim cannot be construed in a vacuum." Tr. of *Markman* Hr'g, Vol. I at 7:17-18.[11] Instead,

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[11] Citations to transcripts refer to the page number followed by the line number of the referenced material.

implored TKT, the Court must interpret the claims in accordance with the specification and the prosecution history and, set in this context, "vertebrate cells" were not meant to encompass human cells even though humans are admittedly a subset of vertebrates. *Id.* at 7:22-25. For the reasons expressed above, however, TKT's contention is untenable. Even if significant intrinsic evidence pointed toward a more limited definition of "vertebrate," "the claim construction inquiry . . . begins and ends in all cases with the actual words of the claim. . . . [T]he resulting claim interpretation must, in the end, accord with the words chosen by the patentee to stake out the boundary of the claimed property." *Renishaw*, 158 F.3d at 1248 (citations omitted). There simply is no hook in the claim term that allows for TKT's alternate construction. The term "vertebrate" is a widely known and understood word which has a precise scientific meaning. A vertebrate is a member of the subphylum Vertebrata, which is a primary division of the phylum Chordata, which in turn is a division of the Animal Kingdom. A vertebrate is uniquely characterized by a segmented bony or cartilaginous spinal cord. Therefore, the plain and ordinary meaning of the term "vertebrate cells," i.e., cells that originate from an animal having a backbone, accords with the words chosen by the patentee to identify the scope of the claimed invention. Because humans are vertebrates, TKT's construction betrays the plain and ordinary meaning of the claim term. Thus, the Court construed the term "vertebrate cells" to mean "cells from an animal having a backbone." Tr. of *Markman* Hr'g, Vol. I at 67:8-9.

B. *Mammalian Cells*

The term "mammalian cells" is contained in Claim 1 of the '422 patent and dependent Claim 9 of the '698 patent. Consistent with its approach to vertebrate cells, TKT proffered a construction of the term "mammalian cells" that excluded human cells. Specifically, TKT contended that "mammalian

cells" are "[c]ells from warm-blooded non-human vertebrate animals whose young are fed by milk secreted from the mammary glands." Defs.' *Markman* Hr'g Demonstrative Ex. 1. Again, with an eye toward literal infringement, Amgen opposed this construction and instead argued that "mammalian cells" are "cells from a warm-blooded animal that has a backbone and whose young are fed by milk secreted from mammary glands." Pl.'s *Markman* Hr'g (Mar. 27, 2000) Demonstrative Ex. 14. For the same reasons explained above, the Court could not remain faithful to the widely known and specific meaning of the word "mammalian" if it were to add the non-human limitation. Simply put, the claim term was not reasonably susceptible to TKT's construction. As a result, the Court determined that "mammalian cells" are "cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands." Tr. of *Markman* Hr'g, Vol. I at 67:9-11.

C. *Mature Erythropoietin Amino Acid Sequence of Fig. 6*

This phrase is contained in Claims 4 and 6 of the '698 patent and Claims 2 and 3 of the '080 patent. Although the phrase sits in different contexts—and thus modifies different subjects—the parties agree that the phrase should have the same meaning in both settings. Focusing on the ordinary meaning of the term "mature," Amgen contended that the phrase means "the fully processed form of the protein secreted by a cell . . . when it transcribes and translates the DNA in Figure 6." *Id.* at 70:24 to 71:4. In contrast, relying on a portion of the specification that explains that "Fig. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues," Trial Ex. 1 at 21:3-5,[12] TKT

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[12] Although the Court did not receive evidence during the *Markman* hearing, for the sake of unity throughout this decision, citations to the patent are made to what was eventually identified as Trial Exhibit 1.

contended that the phrase means "the 166 amino acid sequence of human EPO shown in Fig. 6,"[13] *see* Tr. of *Markman* Hr'g, Vol. I at 90:9 to 102:15. The dispute focused on the amino acid located in the 166th position, arginine. Unknown to Dr. Lin at the time of the invention, arginine is cleaved off at some point during protein synthesis prior to secretion from the cell. Thus, the protein that is actually secreted from the cell contains only 165 amino acids. Figure 6, however, depicts the arginine.

By proffering the language "fully processed," Amgen hoped to obtain an interpretation encompassing the secreted version of the protein, regardless of the specific number of amino acids. Meanwhile, TKT, whose process produces secreted proteins containing only 165 amino acids, sought an interpretation of Figure 6 that specifically required 166 amino acids.

The Court agreed that the term "mature" implied the fully processed form of EPO secreted by the cell, but whether "mature" included the 165 amino acid sequence as well as the 166 amino acid sequence was ambiguous. The patent specification used "mature" to describe an EPO polypeptide that has been secreted by a cell:

> the first residue designated for the amino acid sequence of the mature protein is indicative of the likelihood that EPO is initially expressed in the cytoplasm in a precursor form including a 27 amino acid "leader" region

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[13] TKT's early submissions to the Court regarding claim construction attempted to limit the DNA that encodes the mature erythropoietin amino acid sequence of Figure 6 to "cloned exogenous" human EPO DNA that encodes such sequence. Defs.' Claim Construction Submission (Sept. 20, 1999) at 19. Had TKT continued to press such a construction, the Court would have rejected it for the reasons previously explained. Simply put, no word or words in this disputed claim term are reasonably susceptible of this construction.

> which is excised prior to entry of mature EPO into circulation.

Trial Ex. 1 at 19:36-41. By identifying the EPO that enters circulation as "mature," Dr. Lin essentially defined the term "mature" to mean "the fully processed form of the protein that is secreted by the cell." Consequently, on the one hand, the Court agreed with Amgen's contention that "fully processed" or "fully realized" ought be incorporated into the Court's construction of the phrase "mature erythropoietin amino acid sequence of Fig. 6." On the other hand, the Court was not further persuaded by Amgen that reference to Figure 6 did not limit the meaning of the claim terms to the 166 amino acid sequence disclosed in that figure. Yet neither was TKT able to persuade the Court at the *Markman* hearing that the term was necessarily limited to a 166 amino acid construction. Consequently, the Court chose to abstain for the time being from deciding the "165-166 dispute" and concluded only that the phrase "the mature erythropoietin amino acid sequence of Figure 6" means "the fully realized form of amino acid sequence of Figure 6." Tr. of *Markman* Hr'g, Vol. II at 23:14-18.

D. *Non-human DNA Sequences That Control Transcription and Transcription Control DNA Sequences*

As background, transcription is the process whereby RNA polymerase copies genetic information contained in a DNA nucleotide sequence into a complementary RNA sequence. As the patent explains, "the programming function of DNA is generally effected through a process wherein specific DNA nucleotide sequences (genes) are 'transcribed' into relatively unstable messenger RNA (mRNA) polymers." Trial Ex. 1 at 1:52-55. Transcription is a critical step in the expression of proteins like erythropoietin and is itself controlled by its own DNA sequences. These "transcription control DNA sequences" "precede a selected gene (or series of genes) in a functional DNA polymer [and] cooperate to determine

whether the transcription (and eventual expression) of a gene will occur." *Id.* at 2:10-13. According to the patent, "transcription control sequences" is the collective term for DNA sequences that not only "provide a site for initiation of transcription into mRNA," but also are capable of binding proteins that determine "the frequency (or rate) of transcriptional initiation." *Id.* at 2:3-12. Claims referring to these transcription control sequences were the subject of the following disputes between the parties.

The phrase "non-human DNA sequences that control transcription" is contained in Claim 1 of the '349 patent. Amgen contended that this phrase means "[n]on-human DNA sequences that are able to initiate or regulate RNA synthesis from EPO DNA." Pl.'s *Markman* Hr'g (Mar. 27, 2000) Demonstrative Ex. 69. In contrast, TKT argued that the phrase means "DNA sequences which did not originate in the human genome, which initiate and regulate RNA synthesis of adjacent DNA, and which replace the human EPO transcription control sequences." Defs.' *Markman* Hr'g (Mar. 27-28, 2000) Demonstrative Ex. 1. The dispute centered around a few crucial terms.

First, TKT contended that in order to "control" transcription, the DNA sequences must both initiate *and* regulate the transcription of a gene. Amgen objected to the use of "and," preferring a construction that required DNA sequences either to initiate *or* regulate transcription.

Second, the parties disputed the importance of location. By including the term "adjacent DNA" in its construction, TKT sought to require the DNA sequences that control transcription to be located in a position adjacent to the gene segment intended to be expressed.

Third, the parties disagreed as to the meaning of "non-human." Amgen argued that "non-human" means "not part of the human genome," whereas TKT contended that it means

"not originating in the human genome." Because it is scientifically arguable that viral DNA originates in the human genome, the viral promoter DNA that TKT employs thus might not fall within the meaning of the claim.

The Court first determined that "non-human" DNA sequences are DNA sequences that are "not part of the human genome." Tr. of *Markman* Hr'g, Vol. II at 55:25 to 57:1. The Court rejected TKT's construction, ruling that Amgen meant simply to exclude the human DNA sequences that control transcription from the reach of its claim, sequences which, of course, are part of the human genome. By construing the term "non-human" to mean "not part of the human genome," then, the Court settled on a construction that best effectuated Amgen's intent.

Second, the Court rejected TKT's "adjacent" language because no claim term could reasonably be construed to be limiting the transcription control DNA sequences by their location. Consequently, the Court adopted a construction that was in no way limited by the location of the transcription control sequences relative to the gene to be expressed.

Third, the Court held that "DNA sequences that control transcription are DNA sequences that initiate and may regulate the processes of transcription." *Id.* at 57:1-4. When it announced its construction of this phrase, the Court used the term "may," which signifies that while the DNA sequence must initiate transcription, it need not regulate transcription.

The Court then considered the phrase "transcription control DNA sequences," which is contained in Claim 4 of the '349 patent. Borrowing extensively from the patent specification, the Court explained that "transcription control sequences" are "collectively promoter DNA sequences that provide a site that is capable of initiating transcription . . . and regulator DNA sequences that are capable of binding proteins that determine the frequency or rate . . . of transcription initiation." *Id.* at

57:16-23. At the time, the Court did not recognize the inconsistency between these two constructions. Although "DNA sequences that control transcription" and "transcription control DNA sequences" should have the same meaning, the Court's constructions permitted regulator functions in one instance and required them in the other instance. As will be explained in the infringement portion of the decision, however, the parties tried the case with the latter construction in mind and thus no harm to the parties resulted.

E. *Purified from Mammalian Cells Grown in Culture*

The phrase "purified from mammalian cells grown in culture" is contained only in Claim 1 of the '422 patent, for which the Court subsequently granted summary judgment on literal infringement grounds. The parties presented strikingly different constructions of this phrase during the *Markman* hearing. Amgen contended it means "[p]urified from the in vitro culture in which the mammalian cells have been grown," Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '422 Patent Claim 1, whereas TKT argued that it means "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media," Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 50. TKT admitted that the specification taught three different methods of obtaining EPO: extraction (1) from the cell cytoplasm; (2) from the cell membrane; and (3) from the cell culture medium. TKT nonetheless contended that the plain and ordinary meaning of the phrase meant that the EPO had to be purified from the cells. Thus, argued TKT, Amgen only claimed one of the three methods it taught in the patent. Because TKT obtains its EPO from the cell culture media and not directly from its cells, the parties' positions are not surprising.

The Court, however, disagreed with TKT's interpretation of the claim with respect to both the plain and ordinary meaning of the terms and the consistency of its interpretation

with the other claims. First, TKT's construction would exclude the patent's preferred embodiment: Example 10. Constructions that exclude the patent's preferred embodiment should rarely be adopted. *Modine Mfg. Co.* v. *United States Int'l Trade Comm'n*, 75 F.3d 1545, 1550 (Fed. Cir. 1996); *MediaCom*, 4 F. Supp. 2d at 28. Example 10 extensively describes techniques for obtaining substantially purified erythropoietin from cell culture media. Trial Ex. 1 at 27:15-50, 28:29-32. TKT's claim construction would exclude the method taught in the patent's preferred embodiment and hence is suspect.

Second, from the Court's perspective, TKT's construction ignored the language "grown in culture" and focused solely on the immediately preceding language, "purified from mammalian cells." If the claim merely read "purified from mammalian cells," then TKT's argument that the human erythropoietin must be extracted from the cell itself would indeed have held more sway. Yet all of the terms of the claim must be given effect. Consequently, the Court read the phrase "mammalian cells grown in culture" as a whole and, therefore, as not specifying a particular method, but rather encompassing purification techniques from the cells or the cell culture medium. Thus, the Court held that "purified from mammalian cells grown in culture" means "obtained in substantially homogeneous form from the mammalian cells, using the word from in the sense that it originates in the mammalian cells, without limitation to it only taking it directly out of the interior of the cells, which have been grown in the in vitro culture." Tr. of *Markman* Hr'g, Vol. III at 16:15-19.

F. *DNA Encoding Human Erythropoietin*

The phrase "DNA encoding human erythropoietin" is contained in Claim 1 and related to dependent Claims 3 and 7 of the '349 patent. Amgen, on the one hand, contended that the claim terms are so straightforward that interpretation of

any of the terms was unnecessary. TKT, on the other hand, argued that the phrase means "[h]uman EPO DNA that is exogenous to the cell in which the EPO is produced, i.e., the human EPO DNA did not originate in the genome of the cell into which it is inserted," Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 19—more succinctly, "exogenous DNA encoding human erythropoietin." TKT argued that because the patent specification only taught using DNA that encoded for human erythropoietin that did not originate in the genome of the host cell (exogenous DNA), the claim term should not be interpreted to include both exogenous and endogenous human EPO DNA. Because TKT activates the human erythropoietin gene in the human host cell (the endogenous EPO gene), one can understand TKT's motivation in proffering its construction.

Yet, as the Court pointed out, TKT's construction is merely "a variant of the argument that's already been made here." Tr. of *Markman* Hr'g, Vol. III at 23:2-3. TKT was once again employing invalidity contentions in an attempt to add limitations into claim terms that by their plain meaning were not amenable to such limitations. The plain meaning of the claim terms simply do not call for any such limitation. This portion of the claim language claims any and all DNAs that encode human erythropoietin regardless of such DNA's relationship to the host cell in which it is expressed. Thus, the Court held that "DNA encoding human erythropoietin" means "DNA which encodes human erythropoietin, not including the word exogenous DNA which encodes human erythropoietin." *Id.* at 35:1-3.[14]

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[14] While such a construction, in light of its tautology, probably would neither satisfy a third grade English teacher nor be a sufficient dictionary definition, it was nonetheless more than sufficient to aid the parties and the Court in organizing the presentation of evidence.

G. *Operatively Linked*

"Operatively linked" is located in Claim 4 of the '698 patent and related by dependency to Claims 5 and 9. In context, the phrase relates to the relationship between promoter DNA[15] and the DNA that is transcribed downstream from the promoter DNA. Amgen contended that the phrase means "[p]ositioned such that it provides for initiation of transcription of a gene." Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demontrative Ex. Amgen's '698 Patent Claim 4. TKT argued that the term means "[positioned adjacent] to the DNA encoding EPO in a way that maintains the capability to initiate transcription of EPO DNA." Defs.' *Markman* Hr'g (Apr 10, 2000) Demonstrative Ex. 69 (alteration in original). The parties disputed, once again, the issue of the location of the promoter relative to the gene to be expressed. Amgen argued that the words "operatively linked" imposed no locational restriction, whereas TKT contended that because the patent taught placing the promoter DNA immediately adjacent to the DNA encoding EPO, the term "operatively linked" ought be limited by location.

The term "linked" could, if unmodified by "operatively," imply a spatial relationship in that a link could fix the maximum distance between the two linked objects. Yet modification by the term "operatively" implies a functional rather than physical link between the two objects—in this instance one entity's exertion of influence on another entity. More specifically, in this case, the link between the promoter DNA and DNA encoding EPO consists of the influence possessed by the promoter DNA to initiate the transcription from the DNA encoding EPO. As a result, the term

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[15] Promoter DNA is a segment of DNA that serves to determine where RNA polymerase begins synthesis of RNA from DNA. Here, promoter DNA refers to the DNA segment that determines where RNA polymerase begins the synthesis of RNA that transcribes from the DNA encoding EPO.

"operatively linked" is not defined by the physical location of the promoter DNA relative to the DNA encoding erythropoietin, but rather by the functional effect the promoter DNA has on the EPO DNA. Thus, contrary to TKT's contentions, the term "operatively linked" could not reasonably be construed to impose a locational restriction, because the link is limited only in the sense that the promoter DNA must initiate transcription of the EPO DNA. Consequently, the Court determined that "operatively linked" means "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." Tr. of *Markman* Hr'g, Vol. III at 43:8-10.

H. *Non-naturally Occurring*

The phrase "non-naturally occurring" modifies the erythropoietin glycoprotein product claimed in the '933 patent, Claims 1 and 2 and dependent Claim 9, as well as Claim 3 and dependent Claim 4 of the '080 patent. TKT argued that the phrase was meant to incorporate the exogenous DNA limitation that it had sought (unconvincingly) with respect to many of the prior construed claim terms. Thus, it proffered the following definition: "produced from an EPO DNA coding sequence which was not part of the native genome of the host cell in which the EPO protein is produced. . . ." Defs.' *Markman* Hr'g Demonstrative Ex. 36. Amgen, in contrast, contended that the term means "[o]btained from a source that does not naturally produce or contain EPO." Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '933 Patent Claim 1 (emphasis omitted). The contentions conflicted in this manner because TKT activates an endogenous EPO gene in a human cell, as opposed to generating EPO from an exogenous gene transfected into a host cell.

Unlike the prior instances in which TKT attempted to impose the exogenous DNA limitation into the construction of a claim term, there is a reasonable argument that the term

"non-naturally occurring" has the meaning that TKT attempted to ascribe to it because, to put it simply, there *is* something a bit "non-natural" about an erythropoietin glycoprotein being produced by transfecting host cells with exogenous EPO DNA. Yet TKT's interpretation is deficient for various reasons.

First, TKT's ship runs aground on the claim construction axiom that a claim will not be construed as containing a limitation that is expressed in other claims. *See Karlin Tech. Inc.* v. *Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999). Similarly, "[a]ll the limitations of a claim must be considered meaningful," *Unique Concepts, Inc.* v. *Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991) (citation omitted), and if two separate and distinct limitations are construed as synonymous, the claim recitation of both limitations is redundant and superfluous. *See Beachcombers, Int'l* v. *Wildewood Creative Prods. Inc.*, 31 F.3d 1154, 1162 (Fed. Cir. 1994); *Tex. Instruments, Inc.* v. *United States Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993). Claim 3 of the '933 patent, though not in suit, claims a "non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." If the Court were to adopt TKT's construction of "non-naturally occurring," it would render the terms redundant in the context of the '933 patent's Claim 3. Thus, neither the patentee nor the examiner could have meant the term "non-naturally occurring" to refer to the use of exogenous EPO DNA.

Second, the patent specification also explains that the recombinant-produced and synthetic products are both similar to and different from natural EPO. For example, one passage compares the biological activity of the synthetic products to that of "EPO isolates from natural sources" or "natural EPO isolates." Trial Ex. 1 at 33:14, 33:24; *see id.* at 33:40-44. Thus, the specification indicates that Dr. Lin contemplated his

polypeptide products vis-a-vis the unpatentable EPO polypeptide from natural sources. Furthermore, the Supreme Court has used the term "nonnaturally occurring" to distinguish a "product of human ingenuity" from the "natural phenomenon" that the non-natural version mimics. *See Diamond* v. *Chakrabarty*, 447 U.S. 303, 309-10 (1980). In considering the terms "non-naturally occurring" here, the Court held that Dr. Lin intended a similar meaning. By including this limitation, Dr. Lin meant to stand clear of the unpatentable, naturally occurring products. He intended nothing more.

In light of these considerations, after taking the matter under advisement on April 10, 2000, the Court informed the parties at the final pretrial conference on April 18, 2000 that "non-naturally occurring" means "not occurring in nature."

I. *Glycosylation Which Differs*

The phrase "glycosylation which differs" is recited only in Claim 1 of the '933 patent and relates to Claims 2 and 9 of the same patent by dependency. The parties essentially agreed that glycosylation refers to the carbohydrate side chains that are attached to a molecule, in this case erythropoietin. Yet Amgen further contended that the phrase means that "[t]he attached carbohydrate groups differ when analyzed by standard prior art techniques known as of 1983-84." Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '933 Patent Claim (emphasis omitted). TKT argued that it means "the carbohydrate groups attached to side chains of the erythropoietin polypeptide backbone differ by Western blot analysis and SDS/PAGE[16] and carbohydrate composition

[16] Sodium dodecylsulfate-polyacrylamide gel electrophoresis ("SDS-PAGE") is a widely used procedure for determining the apparent molecular weight of a particular protein or glycoprotein. The Western Blot is a technique for detecting the particular protein or glycoprotein following SDS-PAGE. SDS-PAGE techniques and their relation to glycosylation differences are discussed later. *See infra* Section IV.E.2, at 130-32.

analysis[17] from those of human urinary erythropoietin to at least the degree described in the patents-in-suit. Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 89 (footnotes added). The primary discrepancy concerned which, if any, techniques would be specifically identified as methods encompassed under the meaning of the term "glycosylation which differs." TKT contended that the specification describes two tests by which to prove differences in glycolsylation: SDS-PAGE/Western Blot and carbohydrate composition analysis. Thus, TKT's construction would require proof with respect to both types of tests and no others, whereas Amgen's construction would not limit the manner by which differences in glycosylation are proven.

Example 10 of the patent describes comparisons made between recombinant glycoprotein products and human urinary erythropoietin using various techniques. *See* Trial Ex. 1 at 28:33-67. The specification not only reports data obtained from SDS-PAGE/Western blot analysis, but also by monosaccharide, or carbohydrate, analysis. *See id.* Yet the claim term "glycosylation which differs" is not further limited by the methods used to identify such differences in Example 10. A comparison of Claims 1 and 2 of the '933 patent exposes the significance of the exclusion of such a limitation. Claim 2 of the '933 patent requires the EPO glycoprotein product to have "a higher molecular weight than human urinary EPO *as measured by SDS-PAGE*." *Id.* at 38:23-25 (emphasis added). Claim 1, however, merely states that the erythropoietin glycoprotein product must have "glycosylation which differs from that of human urinary erythropoietin." *Id.* at 38:20-21. The inference is that the patentee knew how to limit claim terms regarding differences in glycosylation by specifying the method by which such differences are

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[17] Carbohydrate analysis reveals the ratio of specific sugars present in a glycoprotein. It is discussed in more detail later. *See infra* Section IV.E.2, at 134-36.

empirically tested. Taking this into account, the Court was loath to mandate that proof of glycosylation differences must be shown using the particular types of tests specifically identified in the patent. As a result, the Court avoided mandatory language, but nonetheless ruled that "glycosylation which differs" means: "Glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." Tr. of *Markman* Hr'g, Vol. III at 102:1823.

J. *Human Urinary Erythropoietin*

The '933 patent employs the phrase "human urinary erythropoietin" in Claims 1 and 2 and dependent Claim 9. Trial Ex. 2 at 38:21, 38:23, 39:3. Amgen contended that the term means "[h]uman EPO isolated from pooled urine of aplastic anemia patients isolated using any method used in the prior art," Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '933 Patent: The Parties Constructions (emphasis omitted), whereas TKT argued that it means "[a]ll EPO preparations that can be isolated or purified from human urine by any method," Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 2. The dispute, then, is essentially one of scope: Does the claim term encompass all erythropoietin preparations obtained from human urine or is it limited to only EPO obtained from the pooled urine of aplastic anemia patients?

In order to support its construction, Amgen relied on the specification and prosecution history. The specification, for instance, identifies and briefly describes the "Miyake procedure"[18] for "purifying human erythropoietin from urine of patients with aplastic anemia." Trial Ex. 1 at 7:10-17. The

[18] The Miyake procedure is a particular method for purifying urinary EPO.

patent cites other prior art sources that describe the isolation of human urinary erythropoietin from the pooled urine of aplastic anemia patients. *Id.* at 8:13-16. The specification also reports the results relating to molecular weight comparisons of CHO-produced EPO, COS-produced EPO, and the "pooled source human urinary extract."[19] *Id.* at 28:33-41. Similarly, Amgen pointed to comparisons between its recombinant erythropoietin and human urinary erythropoietin purified by the Miyake procedure as evidence of novelty. Trial Ex. 2 Tab 6 at 11.

Though Amgen's construction may be supported by these aspects of the specification and prosecution history, Amgen's narrow interpretation of this claim limitation is not faithful to the plain and ordinary meaning of the claim language. The claim terms themselves do not specify which type of human urinary erythropoietin is contemplated. Instead, the plain and ordinary meaning of the phrase "human urinary erythropoietin" broadly encompasses all urinary EPOS. As a result, "on this one, in all candor, the shoe is on the other foot . . . ." Tr. of *Markman* Hr'g, Vol. III at 106:11-12. Thus, adhering to the plain meaning of the terms, the Court concluded that "human urinary erythropoietin" means "erythropoietin derived from human urine." *Id.* at 112:23-24.

III. SUMMARY JUDGMENT OF INFRINGEMENT ON CLAIM 1 OF THE '422 PATENT

Following the *Markman* hearing, the Court turned promptly—albeit in an entirely separate hearing, *see supra* Part II—to considering the then pending motion for summary judgment. On April 26, 2000, the Court heard oral argument regarding whether TKT's activities literally infringe Claim 1 of the '422 patent and Claims 1, 3, 4, and 6 of the '349 patent. Amgen argued that there were no genuine issues of material

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[19] CHO, or Chinese hamster ovary, cells are, as their name suggests, derived from hamsters. COS cells are, in contrast, derived from monkeys.

fact regarding the technologies of each party and that a plain reading of the claims of Amgen's patents entitled Amgen to judgment as matter of law.

Summary judgment is appropriate when there are no genuine issues of material fact and the movant is entitled to judgment as matter of law. Fed. R. Civ. P. 56. Nonetheless, the Court must view the evidence in the light most favorable to the non-movant and must draw all reasonable inferences and resolve all doubts regarding factual issues in favor of the party opposing summary judgment. *Pfaff* v. *Wells Elecs., Inc.*, 5 F.3d 514, 517 (Fed. Cir. 1993). In considering a motion for summary judgment, the Court relies upon any "'pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits'" which, in toto, comprise the relevant record. *Rotec Indus., Inc.* v. *Mitsubishi Corp.*, 215 F.3d 1246, 1250 (Fed. Cir. 2000) (quoting Fed. R. Civ. P. 56[c]). As is required under controlling law, the Court considers only the documents in the summary judgment record as of April 26, 2000.

As this Court has previously held, "if there are no genuine issues of material fact, summary judgment is appropriate in a patent infringement case as in any other." *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107 (D. Mass. 1998). Infringement is a two-part inquiry requiring the construction of the claims, which is a question of law, and the application of the properly construed claims to the allegedly infringing article, which is a question of fact. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996); *Renishaw Plc* v. *Marposs Societa' Per Azioni*, 158 F.3d 1243, 1247-48 (Fed. Cir. 1998).

When the parties do not dispute relevant facts regarding infringement, but merely disagree over claim construction, "the question of literal infringement collapses to one of claim construction and is thus amenable to summary judgment." *Athletic Alternatives, Inc.* v. *Prince Mfg., Inc.*, 73 F.3d 1573,

1578 (Fed. Cir. 1996); *see K-2 Corp.* v. *Salomon S.A.*, 52 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1999). In contrast, when the Court construes the claims in favor of the plaintiff, and a genuine issue of material fact regarding infringement nonetheless exists, summary judgment is not appropriate. *See MacNeill Eng'g Co.* v. *Trisport, Ltd.*, No. 98-12019, slip op. at 17 n.3 (D. Mass. Jan. 10, 2001). With these considerations in mind, the Court addressed the legal issue whether, upon the summary judgment record, TKT's product, HMR 4396, and TKT's R223 cells literally infringe Claim 1 of the '422 patent.

Claim 1 of the '422 patent claims a "pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." Trial Ex. 6 at 38:36-40. As Federal Circuit precedent requires, the Court broke down Claim 1 into each of its limiting terms and compared those terms—and any meanings ascribed to them during the *Markman* hearing—with TKT's HMR4396 and R223 cells.

A. *Pharmaceutical Composition*

Amgen submitted ample and uncontradicted evidence on the summary judgment record that TKT's HMR4396 injection is a pharmaceutical composition. As explained in Section 3.6 of TKT's Investigational New Drug Application ("IND") for HMR4396, which is submitted to the Food and Drug Administration ("FDA") in order to initiate and facilitate the agency's clinical investigation of the product, "HMR4396 Injection is a sterile, nonpyrogenic, colorless aqueous solution in Water for Injection at 4000 U/ml or 10,000 U/ml concentrations." Galvin Decl. (Nov. 4, 1999) Ex. 10 at IND000019. Furthermore, the fact that the product has been submitted for investigation by the FDA is clear evidence that HMR4396 is a pharmaceutical composition. Another IND

document describes diluting the HMR4396 purified bulk "to obtain the desired drug product dosage strengths . . . ." *Id.* Ex. 18 at IND501303; *see id.* Ex. 1 at 242:9 to 243:25, 282:8-21 (explaining that HMR4396 is an aqueous solution that is further formulated into a pharmaceutical composition). In light of this uncontradicted evidence, HMR4396 is a pharmaceutical composition as that term is used in Claim 1 of the '422 patent.

B. *Therapeutically Effective Amount of Human Erythropoietin*

It cannot be disputed that HMR4396 is human erythropoietin. Section 3.3 of the IND for TKT's "Gene-Activated Erythropoietin" directly states that "HMR4396 is human erythropoietin produced by TKT's gene-activation technology." *Id.* Ex. 10 at IND000019; *see id.* Ex. 14 at IND000335-37, 000385 (identifying HMR4396 as human erythropoietin). Furthermore, in response to the question whether HMR4396 is human erythropoietin, TKT's Federal Rule of Civil Procedure 30(b)(6) designee, David S. Johnson, answered affirmatively. *Id.* Ex. 4 at 37:10-11. Another TKT Rule 30(b)(6) designee, Richard F. Selden, admitted that HMR4396 is human erythropoietin. Stretch Decl. (Apr. 20, 2000) Ex. 4 at 399:1519; *see* Galvin Decl. (Nov. 4, 1999) Ex. 1 at 14:12 to 15:6.

In the face of these significant admissions, TKT opted to take two tacks, but neither steadied its rocking boat because both were unsuccessful attempts at changing the Court's claim construction rather than efforts to raise an issue of disputed material fact. First, in its initial response to Amgen's summary judgment motion and during subsequent argument, TKT contended that HMR4396 was not human erythropoietin because as that term is used in the patent "human erythropoietin" means recombinant EPO produced in non-human cells transfected with cloned, exogenous human EPO DNA. Because HMR4396 is produced by activating the endogenous

EPO gene in a human cell, such a construction would exclude TKT's product. This contorted claim construction, however, was rejected by the Court. *See supra* Section II.F, at 33-34.

Second, during oral argument following claim construction, TKT attempted to add a further limitation into the claim. Relying on language from the specification regarding Claim 1 of the '422 patent that explained that the pharmaceutical composition was comprised of "effective amounts of polypeptide products of the invention," Trial Ex. 6 at 12:6-7, TKT argued that "human erythropoietin" should be limited by this phrase. Thus, contended TKT, because the polypeptide products of the invention are defined in part by Figure 6, *see id.* 11:42-54, which erroneously specifies a 166 amino acid chain, *see* Trial Ex. 1 Fig. 6, and TKT only isolates a 165 amino acid product, HMR4396 could not be human erythropoietin. TKT thus seeks to read a 166 amino acid limitation into the claim term "human erythropoietin." This the Court cannot do. As with the previous tack, this argument drifted far astray from the language of the claim and was therefore unpersuasive. Rather than attack the Court's claim construction, to forestall summary judgment, TKT needed to point to *evidence* that would demonstrate a genuine issue of material fact regarding infringement *in the context of* the Court's construction. Because it failed to do so, and Amgen's evidence on the same point was substantial, the Court determined that HMR4396 is human erythropoietin.

Moreover, when asked by the Court whether HMR4396 contains a therapeutically effective amount of human erythropoietin, counsel for TKT admitted that, "If it didn't, believe me, we wouldn't be standing here." Tr. of *Markman* Hr'g, Vol. II at 130:19-20. As admissions on the record constitute evidence upon which reliance may be placed at the summary judgment stage, *see* Fed. R. Civ. P. 56(c), counsel's direct answer is more than sufficient to warrant summary judgment of infringement with respect to this claim term.

Counsel's response also comports with the common sense context of this case. TKT's product would simply pose no real threat to EPOGEN® if it did not contain a therapeutically effective amount of human erythropoietin. Patients would not seek, nor doctors prescribe, such an ineffective product. Viewed in this context, TKT's admission made perfect sense. As a result, the Court determined on the summary judgment record that HMR4396 contained a therapeutically effective amount of human erythropoietin.

C. *Pharmaceutically Acceptable Diluent, Adjuvant, or Carrier*

The evidence on the summary judgment record with respect to HMR4396 showed that it contains a phosphate buffer that acts as a diluent. In particular, as TKT's Rule 30(b)(6) designee explained, once the bulk is generated from the culturing of the human cells, the product is then diluted to provide a product of desired strength. Galvin Decl. (Nov. 4, 1999) Ex. 1 at 243:1219. The diluent is a phosphate buffer that "affords the pH control in the formulation." *Id.* at 243:5-6. The uncontroverted admissions in the Hancock deposition testimony satisfactorily proved that HMR4396 contains a pharmaceutically acceptable diluent, adjuvant, or carrier.

D. *Purified from Mammalian Cells Grown in Culture*

Claim 1 of the '422 patent claims a pharmaceutical composition comprising human erythropoietin that has been purified from mammalian cells grown in culture. Trial Ex. 6 at 38:40-41. In light of the Court's constructions of "mammalian cells" and "purified from mammalian cells grown in culture," *see supra* Section II.B, at 23-24, Section II.E, at 31-33, the Court considers the evidentiary record. The record makes clear that TKT's R223 cell line, which is used to make HMR4396, is derived from an HT1080 cell, which is a human skin cancer cell. Thus, although the cell undergoes a variety of changes during TKT's process, it is—and at all times

remains—a human cell. *See* Galvin Decl. (Nov. 4, 1999) Ex. 4 at 74:14 to 75:12. TKT's approach to this claim term depended entirely on persuading the Court that "mammalian" did not include "human." As explained above, the Court rejected this proffered construction, leaving TKT in the Herculean position of proving that humans were somehow not mammalian. Not surprisingly, they opted instead to concede on the summary judgment record that the R223 cells are mammalian cells under the Court's construction. Tr. of *Markman* Hr'g, Vol. II at 130:21-25. Consequently, the Court determined that TKT employs mammalian cells. *Id.* at 136:1-2.

With respect to the purification process, the evidence on the summary judgment record shows that TKT purifies its EPO from the cell culture supernatant or media rather than directly from the interior of the cells. Stretch Decl. (Apr. 20, 2000) Ex. 3 at 20:18-25. Having failed to convince the Court to adopt its limiting construction of "purified in mammalian cells grown in culture", TKT saw the writing on the wall and, rather than attempt to adduce evidence indicating that TKT did not literally infringe the claim term as it had been construed by the Court, elected to request that the Court reconsider its construction. The Court declined to do so, and as a result, and in reliance on additional summary judgment evidence, it determined that TKT's purification process literally infringed the relevant claim language. *See* Galvin Decl. (Nov. 4, 1999) Ex. 1 at 311:19-25 to 312:2-8; *id.* Ex. 5 at 693:1-16.

E. *Conclusion*

Because HMR4396 is a pharmaceutical composition comprising a diluent and a therapeutically effective amount of human erythropoietin which is purified from mammalian cells grown in culture, the Court ruled on the summary judgment record that HMR4396 infringed Claim 1 of the '422 patent. To this extent, the Court granted Amgen's summary

judgment motion [docket no. 211]. As to all remaining claims under consideration, the Court denied summary judgment.

IV. FINDINGS OF FACT

A. *Parties, Patents, and Products*

Amgen is a Delaware corporation with its principal place of business in Thousand Oaks, California. Joint Pretrial Mem. at 3, ¶ 1. Hoechst Marion Roussel, Inc.—now known as Aventis Pharmaceuticals, Inc.—is a Delaware corporation with its principal place of business in Bridgewater, New Jersey. *Id.* at 3, ¶ 2. TKT is a Delaware corporation with its principal place of business in Cambridge, Massachusetts. *Id.* at 3, ¶ 3. The Court has subject matter jurisdiction over the claims asserted in Amgen's Amended Complaint pursuant to 28 U.S.C. §§ 1338(a) and 2201-02. Venue is proper in accordance with 28 U.S.C. §§ 1391 and 1400 (b).

The five patents-in-suit include the '933 patent, the '698 patent, the '080 patent, the '349 patent, and the '422 patent. *Id.* at 3-4, ¶¶ 5-9. Amgen seeks to enforce the following claims of each patent:

The '933 patent:

> 1. A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.
>
> 2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.

9. A pharmaceutical composition comprising an effective amount a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

. . . .

Trial Ex. 2 at 38:17-25, 39:1-4.

The '698 patent:

4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.

8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

9. The process according to claims 2, 4 and 6 wherein said cells are mammalian cells.

Trial Ex. 4 at 38:39-64.

The '080 patent:

2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.

4. A pharmaceutical composition comprising a therapeutically effective amount an erythropoietin glycoprotein product according to claim 1, 2, or 3.

. . . .

Trial Ex. 3 at 38:39-53.

The '349 patent:

1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of pro-

ducing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin.

. . . .

3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.

. . . .

6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

7.A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Trial Ex. 5 at 38:8-14, 38:18-27, 38:31-36.

The '422 patent:

1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

Trial Ex. 6 at 38:36-40.

In conjunction with his research team, Amgen scientist Dr. Fu-Kuen Lin was the inventor of the inventions claimed in this group of patents. *See* Trial Tr. at 957:21 to 958:18. Amgen owns all five patents by assignment. Trial Exs. 140-49. All five patents share a common disclosure and specification while the claims, of course, vary. *See* Joint Pretrial Mem. at 4, ¶ 10.

Amgen manufactures and sells a human erythropoietin pharmaceutical product known as epoietin alfa under the trademark EPOGEN®. Trial Tr. at 957:8-11. Specifically, EPOGEN® is the product of Example 10 of the patents-in-suit. *See id.* at 957:818, 1044:9-20.

In collaboration with TKT, Hoechst is developing HMR4396. *See* Joint Pretrial Mem. at 4, ¶ 12. HMR4396 is human erythropoietin. *See supra* Section III.B, at 48-50. HMR4396 is produced from the R223 cell line grown in culture. Joint Pretrial Mem. at 4, ¶ 13. Lonza Biologics, Inc. manufactures HMR4396 in the United States under a contract between TKT and Lonza Biologics PLC (the parent company of Lonza Biologics, Inc.). *Id.* at 4, ¶ 14. Using HMR4396 produced in the United States, Gruppo Lepetit, S.p.A. in Anagni, Italy currently formulates HMR4396 Injection. *Id.* at 4, ¶ 16. Ben Venue Laboratories, Inc. previously formulated HMR4396 Injection in the United States pursuant to a contract between TKT and Ben Venue. *Id.* at 4, ¶ 15. TKT intends to file a Biologics License Application for HMR4396 with the FDA. *Id.* at 4, ¶ 17. In addition, it is seeking regulatory approval to make and sell HMR4396 produced from the R223 cell line in the United States. *Id.* at 4, ¶ 18. TKT is the sponsor of the Investigational New Drug application for HMR4396. *Id.* at 4, ¶ 19.

B. *The Biological Activity of Erythropoietin*

As explained in the patent specification:

> Erythropoiesis, the production of red blood cells, occurs continuously throughout the human life span to offset cell destruction. Erythropoiesis is a very precisely controlled physiological mechanism enabling sufficient numbers of red blood cells to be available in the blood for proper tissue oxygenation, but not so many that the cells would impede circulation. The formation of red blood cells occurs in the bone marrow and is under the control of the hormone, erythropoietin.

Trial Ex. 1 at 5:39-47. In more basic terms, hemoglobin is the protein in red blood cells that transports oxygen. Trial Tr. at 1674:8-10. The amount of hemoglobin in the body correlates to the amount of oxygen that can be supplied to the body's tissues. *Id.* at 1674:11-14. Hematocrit is a measurement of the ability of the blood to supply oxygen to the body. *Id.* at 1674:15-17. Hematocrit level indicates the relative proportion of red blood cells to the total volume of blood. *Id.* at 1674:18-21. An increase or decrease in the hematocrit or hemoglobin results in an increase or decrease in the ability of the blood to supply oxygen to the body. *Id.* at 1674:22 to 1675:4. Under normal conditions, forty-five to fifty percent of the blood is made up of red blood cells, and in such circumstances, the hematocrit would be referred to as forty-five to fifty. *Id.* at 1570:24 to 1571:2.

Anemia occurs when a person does not have a steady, sufficient supply of red blood cells to carry oxygen to all the tissues of the body. *Id.* at 1674:4-7. Thus, the primary cause of anemia incident to chronic renal failure is a decrease in the production of red blood cells in the patient's blood. *Id.* at 1676:15 to 1677:5. The first medical condition for which erythropoietin was shown to be therapeutically effective as a pharmaceutical composition was this type of anemia. *Id.* at

2769:18-21. The therapeutic goal for treating patients with chronic renal failure is to increase and maintain the production of red blood cells in the patient's blood to normal or near normal levels. *Id.* at 1675:5-20. By increasing and maintaining the patient's hematocrit to normal or near normal levels, the ability of the patient's blood to provide a steady supply of sufficient oxygen to body tissues can be restored. *Id.* at 1681:11-15, 18-20. In order to correct the anemia incident to chronic renal failure, a sustained increase in hematocrit or hemoglobin to normal or at least near normal levels is required. *Id.* at 1681:18-20, 1688:25 to 1689:4. The therapeutic effectiveness or benefit of an erythropoietin preparation is shown by demonstrating a correction in anemia by increasing and maintaining the hematocrit of a patient to normal or near normal levels. *Id.* at 2763:4-8, 2777:14 to 2778:8. Measurements of hematocrit and hemoglobin were included in the first clinical trials involving recombinant erythropoietin ("rEPO") to allow physicians to determine if a treatment with erythropoietin had been effective. *Id.* at 1689:15-23. In those trials, rEPO was determined to be therapeutically effective because it was able to increase and maintain the patients' hematocrit level to thirty-five to forty percent. *Id.* at 2770:20-24, 2773:13-22, 2774:5-7. Furthermore, in conjunction with TKT's clinical trials of HMR4396 Injection, the FDA has rejected mere increases in hemoglobin as a meaningful therapeutic endpoint, and instead has insisted that TKT test for a sustained increase in hemoglobin over a minimum twelve-week period. *See* Trial Ex. 198; Trial Tr. 2254:8 to 2255:24.

C. *Judgment of Non-infringement of the '080 and '698 Patents*

Trial commenced on May 15, 2000. Following opening statements and pursuant to the schedule agreed upon during the April 18, 2000 final pretrial conference, *see* Fed. R. Civ. P. 16(a), Amgen began its infringement case. When Amgen

rested on the issue of infringement, TKT moved for judgment on partial findings, *see* Fed. R. Civ. P. 52(c), contending that (1) Amgen's infringement evidence was fatally deficient with respect to certain claims; and (2) judgment of non-infringement on those claims ought be issued. Following oral argument on June 9, 2000, the Court granted judgment of literal non-infringement with respect to the claims in suit of the '080 and '698 patents and judgment of non-infringement under the doctrine of equivalents with respect to the '698 patent. The factual findings[20] undergirding these conclusions are set forth below.

1. *'080 Patent*

On June 9, 2000, the Court found as matter of fact that there was no literal infringement of Claims 2, 3, and 4 of the '080 patent. In summary, the asserted claims of the '080 patent claim not only an erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, but also a pharmaceutical composition comprising a therapeutically effective amount of such glycoprotein.[21] In addition, the glycoprotein is further limited because in all the relevant claims it must comprise "the mature erythropoietin amino acid sequence of FIG. 6." Trial Ex. 3 at 38:42-43, 49-50. The Court had construed this highly significant phrase to mean "the fully realized form of the amino acid sequence

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[20] The Court made clear on the record that Amgen "introduced sufficient evidence as matter of law to warrant a finding by the Court of infringement." Trial Tr. at 1305:22-23. Thus, in subsequently finding that Amgen failed to persuade the Court by a fair preponderance of the evidence on these issues, the Court was acting entirely in its capacity as fact finder.

[21] Claims 2 and 3 are independent claims devoted to the erythropoietin glycoprotein, and Claim 4 is a dependent claim involving a pharmaceutical composition comprising the glycoprotein product according to Claims 2 and 3. Trial Ex. 3 at 38:39-53.

of Figure 6." Tr. of *Markman* Hr'g, Vol. II at 23:14-18. At the time of the *Markman* hearing, the determination of what, in fact, comprised the Figure 6 limitation was left for another day. *Supra* Section II.C, at 24-27. That day arrived when the Court was required to apply the claim construction to the factual record.

The patent specification's Figure 6 contains a significant amount of information on a number of levels that the parties do not dispute. Figure 6 displays the nucleotide series or DNA sequence of human erythropoietin including both exons (the portions of the sequence which code for the desired protein) and introns (the portions of the sequence that do not code for the protein and are spliced out during transcription into mRNA). *See* Trial Ex. 1 at 20:39 to 21:2. Figure 6 also sets apart a series of "codons," which are sets of three adjacent nucleotides that determine which of the twenty amino acids are incorporated into a protein at a particular location. Each amino acid is identified by its three letter abbreviation representing a codon. Figure 6 thus depicts the deduced amino acid sequence, which is arrived at by reading the codons of the DNA encoding the protein. Figure 6 also numbers the amino acids from -27 to 166. The span begins with a negative number because the negative amino acids represent the signal or leader peptide which is cleaved off in the rough endoplasmic reticulum prior to the protein's secretion from the cell. The numbers then continue from 1 to the final amino acid at position 166, which is labeled arginine. As will soon be apparent, it seems safe to say that never before has one arginine been so significant in a court of law.

Key language in the patent specification describes what is depicted by Figure 6: "FIG. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues . . . ." *Id.* at 21:3-5. This language equates the amino acid sequence of mature human EPO with the specifically

enumerated 166 amino acid sequence that is disclosed in Figure 6. *Id.* In this light, it can scarcely be doubted that the "mature erythropoietin amino acid sequence" is the sequence depicted in Figure 6. Had Amgen claimed only "the mature erythropoietin amino acid sequence" without associating or linking that amino acid sequence to Figure 6 its argument that its claims cover whatever sequence (whether it contained 165 or 166 amino acids) is ultimately secreted by the cell might have more momentum. Yet because the asserted claims are limited explicitly by the meaning of Figure 6, the specific amino acid sequence displayed therein is significant. Amgen's attempt to persuade the Court that the claims reciting the amino acid sequence of Figure 6 reach the mature (i.e., fully realized or secreted) form of the protein, but are not further restricted by the specified amino acid sequence depicted in Figure 6 fails. As a result, in order to infringe Claims 2 and 3 of the '080 patent (and Claim 4 by dependence) literally, HMR4396 must contain an erythropoietin glycoprotein comprising the fully realized erythropoietin amino acid sequence of Figure 6, which depicts 166 amino acids.

With this claim construction, the Court turns to the trial testimony. During the trial, Dr. Harvey Lodish, a research biologist from the Whitehead Institute and the Massachusetts Institute of Technology, *see* Trial Tr. at 40:11-16, testified forthrightly about Figure 6 and specifically about the number of amino acid residues that comprise the erythropoietin protein. First, there is no dispute that the amino acids labeled 1 through 165 in Figure 6 are the same 1 through 165 that are contained in HMR4396. *Id.* at 202:14-16; *id.* at 348:10-12; Trial Ex. 25 at IND002357. During cross examination, however, Dr. Lodish and TKT's counsel had the following exchange:

> Q: You agree that Figure 6 displays an amino acid sequence of 166 amino acids?

A: It does. And—yes, it does. It certainly does.

Trial Tr. at 347:16-18. Dr. Lodish explained the discrepancy between Amgen's Figure 6 and the 165 amino acid sequence of the secreted EPO:

> What is missing is the arginine at position 166, and that is because, as I testified, that arginine is present on the initial protein made by the ribosomes in the cells and it is removed by the cell before the protein is secreted, and that is why I have 165.

Id. at 348:3-9. In fact, his testimony further reveals that at the time the patent was written, it was not yet known that the arginine at the carboxyl terminus was cleaved off prior to secretion of the protein from the cell. *Id.* at 350:20 to 351:4. But of particular importance in light of the Court's interpretation of Figure 6, during direct examination by Amgen's counsel, Dr. Lodish explained that "HMR4396 is a glycoprotein containing 165 amino acids." *Id.* at 200:21-22 (quoting Trial Ex. 18 at IND000019). Such a glycoprotein literally does not infringe a patent claim that specifies a 166 amino acid sequence. Consequently, at the close of Amgen's infringement case, the Court found that HMR4396 does not literally infringe Claims 2 and 3 (as well as Claim 4 by dependence) of the '080 patent.[22] *Id.* at 1306:19-23.

2. *'698 patent*

Also on June 9, 2000, the Court granted judgment of non-infringement with respect to the '698 patent, both literally and under the doctrine of equivalents. The asserted claims of the '698 patent address the process by which glycosylated erythropoietin polypeptides having certain characteristics are produced. Claims 4 and 6 are independent and Claims 5, 7, 8,

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[22] The Court denied the motion for judgment of non-infringement under the doctrine of equivalents on the '080 patent. *See* Trial Tr. at 1306:23-25.

and 9 are dependent. Because the Court was not persuaded by a preponderance of the evidence that TKT infringes Claims 4 and 6, judgment of non-infringement as to all of the asserted claims of the '698 patent is hereby entered.

In considering the '698 patent, the Court notes an important distinction between product patents on the one hand and process patents on the other. A product patent claims a structural entity that, though some process must be undertaken in order to create it, is in no way defined or limited by how it is made. *See Procter & Gamble Co.* v. *Berlin Mills Co.*, 256 F. 23, 29 (2d Cir. 1919); *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 706 F. Supp. 94, 103 (D. Mass. 1989). A process patent, however, claims not a structural entity, "but rather an operation or series of steps leading to a useful result." 1 *Chisum on Patents* § 1.03, at 1-58 (2000). Thus, the very details regarding how such "useful result" has come about are at the heart of a process patent, whereas the process by which a patented product is obtained is ordinarily irrelevant to a product patent.

This distinction between product and process patents plays itself out in the context of the set of patents owned by Amgen and asserted in this litigation. The cells, glycoproteins, and pharmaceutical compositions protected by the '349, '933, '080, and '422 patents are all structural entities. They are therefore products and the patents that protect them are product patents. In contrast, the processes claimed in the '698 patent are different beasts all together. The claims of the '698 patent recite a series of steps that, if followed by one skilled in the art, will produce an identified useful result. Thus, unlike the product claims, for which it does not matter how one reached the patented result provided that the same (or substantially equivalent) result has been reached, *how one reaches the useful result* is the very substance of a process patent.

To put meat on these abstractions, compare the '349 patent with the '698 patent. Claim 1 of the '349 patent describes a

certain entity—a type of cell that has additional specific characteristics. In order to avoid infringing that product claim a competitor must not make that product regardless whether the process used to do so differs in some way from the process or processes described in the patent. If indeed the same product is ultimately obtained, it matters not that in order to do so the competitor tweaked the process in some manner. Of course, if the rule were any different, then product claims would easily be thwarted by even the most minuscule methodological modifications. Such a doctrine would render patent protection meaningless.

In contrast, *by its very nature as a process patent*, the '698 patent requires those skilled in the art to familiarize themselves with the details of the process for the production of recombinant glycosylated erythropoietin polypeptides. The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything. Thus, in the '698 patent the devil is in the methodological details.

Based on this understanding of process patents, the many differences between Amgen's and TKT's processes, that were often admitted by Amgen's witnesses, rendered Amgen's proof of infringement on the '698 patent insufficient to survive TKT's Rule 52(c) motion. In short, the Court was not persuaded by a preponderance of the evidence that TKT's process for making GA-EPO (TKT's EPO product) infringed, either literally or by substantial equivalent, independent Claims 4 and 6 of the '698 patent. As a result, judgment of non-infringement will also be entered on dependent Claims 5, 7, 8, and 9. The Court now turns to these key methodological distinctions.

Among the variety of distinctions, two aspects of TKT's process stand out from Amgen's. First, and most funda-

mentally, TKT employs homologous rather than heterologous recombination. In order to make EPOGEN®, Amgen transfects Chinese hamster ovary ("CHO") cells with a vector that contains both viral promoter DNA and the human EPO gene. *See* Trial Ex. 1 at 25:55-61; Trial Tr. at 375:4-9. Thus, relative to the hamster host cell, the human EPO DNA material is exogenous because it has been removed from the cell in which it originated, placed in a vector, and reintroduced into a host cell. Trial Tr. at 174:18-22, 1330:2-5. In fact, the only type of recombination shown in Amgen's examples in the patent is heterologous. Trial Tr. at 375:19-25, 376:25 to 381:1. In order to make GA-EPO, however, TKT does not utilize a host cell from a non-human species. *See id.* at 165:19-21. Instead, TKT manipulates the human EPO gene where it naturally resides in an HT1080 human cell line. *Id.* at 165:21. In that sense then, the human EPO gene is endogenous to the human cell. *Id.* at 174:23 to 175:4. Thus, in TKT's process, after introducing a promoter sequence, human EPO is expressed in a human rather than hamster cell.

The Amgen patent specification's repeated references to exogenous DNA reveals that the Amgen process was directed toward heterologous rather than homologous recombination. The patent announces, for example, that "[t]hese polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA [complementary DNA] cloning or by gene synthesis." Trial Ex. 1 at 10:15-20. The Amgen patent specifications also explain in summarizing what is depicted in Example 10 that:

> Example 10 is directed to a development of mammalian host expression systems for . . . human species genomic DNA involving Chinese hamster ovary ("CHO") cells and to the immunological and biological activities of

> products of these expression systems as well as characterization of such products.

Id. at 15:4-9. Here, Amgen makes plain that DNA material from one species and the cells from another have been utilized in order to effectuate expression. Amgen also specifically identified the content of the transfected vector, which included the human EPO gene, and the type of cell hosting the transfection, the CHO dihydrofolate reductase ("DHFR")[23] cells. *Id.* at 25:51-59. There can be no dispute that the process most heavily relied upon by Amgen in its patent is the transfection of exogenous DNA. This process, however, is not the one performed by TKT in making GA-EPO nor is it substantially similar to TKT's process. Instead, TKT is able to express high levels of human EPO in human cells without having to rely upon host cells from alternative species, an important distinction in the eyes of the Court.

A second distinction that the Court finds material to whether TKT's process infringes the two independent claims of the '698 patent concerns where the promoter DNA is located relative to the gene to be expressed. In the patent specification, Amgen described the exact location where the human EPO genetic fragment was cleaved in the process of creating the plasmid vector to be introduced into the host cell. *Id.* at 24:19-22. As explained in Example 7 and illustrated in Figure 4, Amgen created the vector by cleaving, with BstEII restriction endonucleases, within the 5.6 Kb EPO gene "at a position which is 44 base pairs 5' to the initiating ATG coding for the pre-peptide and approximately 680 base pairs 3' to the HindIII restriction site." *Id.* Dr. Lodish agreed that Amgen's endonucleases cleaved off genetic material at a position forty-four base pairs from the first codon that expresses the leader

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[23] The DHFR gene is a marker gene that allows for the selection of cells that have amplified copies of the gene.

peptide. *See* Trial Tr. at 372:14-19. Furthermore, the patent specification reports:

> The genomic human EPO gene can be isolated therefrom as a 4900 base pair BamHI digestion fragment carrying the complete structural gene with a single ATG 44 base pairs 3' to BamHI site adjacent the amino terminal coding region.

Trial Ex. 1 at 24:28-32. Thus, Amgen's process makes a point of leaving but one ATG in the region to be expressed. An ATG is often the codon where the ribosome attaches and where, therefore, protein synthesis initiates.

TKT, however, does something different. TKT inserts its CMV promoter and enhancer farther upstream than the position at which Amgen inserts its SV40 promoter. Thus TKT's process has within the DNA sequence upstream of the codons that express the EPO polypeptide several ATG sites. *See* Trial Tr. at 537:18-20. Despite the concern that these additional ATG sites might interfere with proper protein synthesis, TKT attaches its CMV promoter so many bases upstream that a number of these ATGs are present between the promoter and leader peptide. The Court finds that such a process is sufficiently different from that encompassed by Amgen's invention that judgment of non-infringement should follow.

In particular, the Court finds that the technique of placing the promoter in close proximity to the gene intended to be expressed was believed, by those of ordinary skill in the art in 1984, to be the technique most likely to result in the proper transcription of that gene. Amgen's patent itself teaches as much in Example 7. *See* Trial Ex. 1 at 24:15-32. Dr. Lodish's testimony does nothing to alter this conclusion. Dr. Lodish testified with respect to the promoter issue that "[w]hat is important is that if I put the SV40 promoter in this case, or perhaps other promoters, upstream of the EPO gene I will make EPO, and that's the critical issue." Trial Tr. at 549:

10-13. Yet, he shied away from definitively rejecting the idea that the location of the promoter relative to the desired gene was important. Instead, referring to the distance between the promoter and the gene to be expressed, he testified cautiously that "how far away from it, *perhaps* is not critical." *Id.* at 549:9-10 (emphasis added). Furthermore, Dr. Lodish seemed to be testifying, at least on this precise point, from his understanding of today's technology. He made no statement implying that one of ordinary skill in the art in 1984 would dare to place a promoter sequence in such a position that multiple ATGs would exist between it and the gene to be expressed. Thus, the process that Amgen described in its patent specification was one characterized by the placement of the promoter DNA in a position *adjacent* to the EPO leader peptide. Because TKT's process is more technologically advanced because it does not require the more immediate adjacency of the promoter, the Court finds that TKT's process for expressing the EPO protein in abundance is substantially different from the process identified in Amgen's '698 patent. As a result, Amgen has failed to prove by a preponderance of the evidence that TKT's process infringes the independent claims of the '698 patent.

Thus, because of TKT's use of both endogenous rather than exogenous DNA and a viral promoter located far upstream from the EPO coding region, as well as other less fundamental distinctions, TKT is entitled to judgment of non-infringement on the '698 patent both literally and under the doctrine of equivalents.

D. *Anticipation and Obviousness (Prior Art)*

After the Court rendered its findings and conclusions as to the partial judgment of non-infringement, TKT proceeded to present its case as to the remaining issues. At the conclusion of TKT's rebuttal case, Amgen moved for judgment of infringement and judgment of validity in separate motions. The motions were heard together on July 21, 2000, and at the

conclusion of the hearing, the Court made certain findings under Rule 52(c). While the Court declined to make any determinations on the remaining issues of infringement, Trial Tr. at 2532:7-8, the Court found that TKT had failed to carry its burden of proving its obviousness and anticipation defenses by clear and convincing evidence, *see id.* at 2534: 7-10. The required subsidiary findings and rulings follow.

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. It comes as a surprise to no one that inventions must be new. "The novelty requirement lies at the heart of the patent system." 1 *Chisum on Patents* § 3.01, at 3-3. Section 102 helps to define this novelty requirement. It provides that:

> A person shall be entitled to a patent unless—
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention by the applicant for patent, or
>
> . . . .
>
> (e) the invention was described in—
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent . . . , or
>
> (g) (2) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it . . . .

35 U.S.C. § 102. Thus, in order to negate the patent holder's claim of novelty by the use of prior art, one must show evidence of a prior patent or publication anywhere or prior use, knowledge, or invention in the United States. An invention is anticipated if it was known, used, patented, described,

or made by another prior to the applicant's invention thereof. *See* 1 *Chisum on Patents* § 3.02, at 3-6.

1. *Anticipation*

"[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc.* v. *Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citing *Atlas Powder Co.* v. *Ireco Inc.*, 190 F.3d 1342, 1347 [Fed. Cir. 1999]; and *In re Paulsen*, 30 F.3d 1475, 1479 [Fed. Cir. 1994]). The identical invention must be shown in a single prior art reference in as complete detail as contained in the patent. *Richardson* v. *Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Furthermore prior art reference must be enabling, thus placing the claimed invention in the possession of the public. *Akzo N.V.* v. *United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986). "Anticipation, put simply, requires that every element of the claimed invention was previously 'described in a single reference.'" *Advanced Display*, 212 F.3d at 1283 (quoting *Scripps Clinic & Research Found.* v. *Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Moreover, if the Patent Office considered a particular prior art reference, then the challenger has the "added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." *Am. Hoist & Derrick Co.* v. *Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984); *see Ultra-Tex Surfaces, Inc.* v. *Hill Bros. Chem. Co.*, 204 F.3d 1360, 1367 (Fed. Cir. 2000).

Determining whether a prior art reference has anticipated a patented invention is matter of fact. *Advanced Display*, 212 F.3d at 1283. TKT bears the burden of proving invalidity by anticipation by clear and convincing evidence. *Robotic Vision Sys.* v. *View Enq'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir.

1999). Clear and convincing evidence is "evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions is 'highly probable.'" *Buildex, Inc.* v. *Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988).

a. *EPO-Producing Human Tumor Cells*

TKT contended that the cells described in a series of references anticipate certain Amgen claims because the references describe human tumor cells that produce EPO.[24] Among these nine references are Kaname Sugimoto's United States Patent No. 4,377,513 (the '513 patent), which identifies a process for the production of human erythropoietin from lymphoblastoid cells,[25] and an article by Masamichi

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[24] These are the references: J.L. Ascensao et al., *Erythropoietin Production by a Human Testicular Germ Cell Line*, 62 Blood 1132-34 (1983) (Trial Ex. 2425); Masamichi Hagiwara et al., *Erythropoietin Production in Long-term Cultures of Human Renal Carcinoma Cells*, 154 Exp. Cell Res. 619-24 (1984) (Trial Ex. 2428); Tsunehiro Saito et al., *Translation of Messenger RNA from a Renal Tumor into a Product with the Biological Properties of Erythropoietin*, 13 Exp. Hematol. 23-28 (1985) (Trial Ex. 2427); T. Saito et al., *Translation of Human Erythropoietin-mRNAs*, 11(14) Exp. Hematol. 228 (1983) (Trial Ex. 2426); Judith B. Sherwood & Daniel Shouval, *Continuous Production of Erythropoietin by an Established Human Renal Carcinoma Cell Line: Development of the Cell Line*, 83 Proc. Nat'l Acad. Sci. USA 16569 (1986) (Trial Ex. 2424); J.B. Sherwood et al., *Establishment of a Human Erythropoietin-Producing Renal Carcinoma Cell Line*, 31 Clinical Res. 163A (1983) (Trial Ex. 2432); Kaname Sugimoto, *Process for the Production of Human Erythropoietin*, United States Patent No. 4,377,513 (issued Mar. 22, 1983) (Trial Ex. 2374); Tomoyuki Tajima, Japanese Patent Application Kokai Number: SHO 54-55790 (1979) (Trial Ex. 2423); Keisuke Toyama et al., *Erythropoietin Levels in the Course of a Patient With Erythropoietin-Producing Renal Cell Carcinoma and Transplantation of This Tumor in Nude Mice*, 54 Blood 245-53 (1979) (Trial Ex. 2249).

[25] A lymphoblastoid cell is a cell typically isolated from a patient with leukemia, which is a cancer of the blood. Trial Tr. at 1795:20-22.

Hagiwara et al., which reports the isolation of erythropoietin from human renal carcinoma cells. *See* Trial Exs. 2374, 2428. Dr. Erslev, a witness proffered by TKT, agreed that the remaining seven references report cells that are essentially the same as those identified in Hagiwara's report, *see* Trial Tr. at 1743:21 to 1744:18. After examining these references, the Court agreed with Dr. Erslev. In each case, the researchers surgically removed tumor tissues from cancer patients who had high levels of EPO production, and then cultured those cells in order to try to detect erythropoietic activity. *See* Trial Exs. 2249, 2423-27, 2432. Amgen's patent specification specifically disclosed the Sugimoto patent and identified another article by Hagiwara that reported the same results. Trial Ex. 1 at 7:24-42.

Amgen's disclosure of two references that are representative of the work in this area gives rise to the notion that "the burden of proving invalidity is especially heavy" when the defendant relies on "art that has previously been considered by the patent office during prosecution of the patent application." *Pall Corp.* v. *Micron Separations, Inc.*, 792 F. Supp. 1298, 1314 (D. Mass. 1992), *aff'd in part, rev'd in part*, 66 F.3d 1211 (Fed. Cir. 1995); *see Am. Hoist*, 725 F.2d at 1359. Although this burden is not insurmountable, TKT failed to overcome it.

First, the Court considered whether these references constituted "prior art." Amgen submitted that two of these nine references failed to satisfy the touchstone element of the prior art defense: that the art was in fact prior. Amgen argued that the "printed publication" of the references was subsequent to Amgen's date of invention. *See* 35 U.S.C. § 102(a). The 1986 Sherwood and Shouval reference concerning production of EPO in human renal carcinoma cells was published years after the time necessary to be considered a prior art publication. Trial Ex. 2424; *see* 35 U.S.C. § 102(b). Likewise, the Saito et al. reference regarding EPO

activity in renal tumor cells grown in culture was published in 1985, Trial Ex. 2427, a year after the last of Amgen's patent applications was submitted to the Patent Office. While the document does bear the words, "Received 18 August 1983; accepted 18 July 1984," *id.*, TKT has failed to persuade the Court that either of these earlier dates should be considered the appropriate date of the "printed publication." 35 U.S.C. § 102(a). To qualify as a "printed publication" under section 102, a party must show accessability and availability to those skilled in the art. *Carella* v. *Starlight Archery & Pro Line Co.*, 804 F.2d 135, 139 (Fed. Cir. 1986). The fact that a reference was received by a publication does not evidence that it was either available or accessible. Consequently, neither of these articles constitute a prior art publication.

Yet as the statute makes clear, there is more than one way to skin the prior art cat. If the invention is made, used, or known in the United States prior to invention by the patent holder, then it has been anticipated. 35 U.S.C. § 102(a), (g). Thus, the fact that the 1985 Saito et al. and 1986 Sherwood and Shouval references were published after the filing of Amgen's patent applications does not alone render the work described in those references inadequate for anticipation purposes. Instead, the Court finds that the Sherwood and Shouval and Saito et al. references evidence that the work performed by the researchers was done in the United States prior to Amgen's breakthroughs in late 1983 and 1984. *See* Trial Exs. 2424, 2427. The Sherwood and Shouval reference reports that their human renal carcinoma cell line had maintained its EPO-producing function continuously since 1981. Trial Ex. 2424 at 165. Though it is not explicitly mentioned in the article, the Court infers from Dr. Sherwood's Bronx, New York business address that her work was performed in the United States. *Id.* Similarly, the work reported in the 1985 Saito et al. reference appears to have been performed at the University of Tennessee College of

Medicine in Knoxville sometime prior to August of 1983. Trial Ex. 2427 at 23.

Beyond the fact that the work appears to have been performed somewhere in the United States prior to Amgen's work, the knowledge or use of the work must also be accessible to the public. *See Carella*, 804 F.2d at 139. "A prior use is sufficient to anticipate a patent if it involves work done openly and in the ordinary course of business activities without any deliberate attempt at concealment or effort to exclude the public, even though no deliberate act was taken to bring the work to the attention of the public at large . . . ." *State Indus., Inc.* v. *Rheem Mfg. Co.*, No. 3-83-0362, 1984 WL 1243, at *18 (M.D. Tenn. June 5, 1984), *aff'd in part, rev'd in part*, 769 F.2d 762 (Fed. Cir. 1985) (reversing on inequitable conduct and award of attorneys fees). Rather than requiring widespread public use or knowledge, section 102(a) only requires courts to examine whether prior inventors made deliberate efforts to conceal (or otherwise exclude the public from) their inventive work. *See W.L. Gore & Assocs., Inc.* v. *Gorlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983). If they did not, and instead performed their work openly and in the ordinary course of business, then their use (and by implication, knowledge) should be considered accessible to the public. *See Elec. Storage Battery Co.*, v. *Shimadzu*, 307 U.S. 5, 20 (1939); *Baxter Int'l, Inc.* v. *COBE Lab., Inc.*, 88 F.3d 1054, 1058 (Fed. Cir. 1996). Because the record contains no evidence to suggest that Saito or Sherwood and their colleagues took any actions to shield their work from others, the Court finds that the knowledge and use of the work that was subsequently described in the two references meets the requirements of section 102(a). As a result, the EPO-producing tumor cell work described by the Sherwood and Shouval and Saito et al. references qualifies as prior art, though it remains to be seen whether this art anticipates any of Amgen's claims.

The second step in an anticipation analysis involves a comparison of the construed claim to the prior art. A prior art reference must disclose "each and every limitation of the claimed invention . . . must be enabling[,] and [must] describe . . . [the] claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *In re Paulsen*, 30 F.3d at 1478-79.

After comparing the construed claim with the 1983 Saito et al. reference, the 1983 Sherwood et al. reference, and the never-issued patent application of Tajima, Trial Exs. 2426, 2432, 2423, the Court was unpersuaded that the references described or enabled "the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *Helifix Ltd* v. *Blok-Lak, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000); *see Advanced Display Sys., Inc.* v. *Wu*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Further, TKT failed to elicit persuasive testimony from its witnesses that showed that one of ordinary skill in the art could produce Amgen's cells after examining any of these references. Moreover, although not dispositive, these references were never scrutinized by the scientific community. Both the 1983 Sherwood et al. and 1983 Saito et al. references were simply abstracts and were not peer reviewed prior to publication. Absent the close and careful scrutiny afforded by such review, the abstracts lack significant persuasive punch. Similarly, the unexamined, never-issued Tajima patent constitutes nothing more than unchallenged scientific claims. In contrast, an issued patent stands on far more solid footing because it has been scrutinized and challenged by an examiner trained in the field in which the patent teaches.

To further support its anticipation defense, TKT relies most heavily on Sugimoto's '513 patent. *See* Trial Ex. 2374. Recall that the '513 patent, as well as Sugimoto's related work, was disclosed in Amgen's patent specification. *See* Trial Ex. 1 at 7:24-35. In light of the subsequent issuance of Amgen's

patents, the Patent office clearly concluded that this reference was not anticipating. Nonetheless, it was open to TKT to persuade the Court that the examiner erred. Ultimately, however, TKT could not carry its burden of proof by clear and convincing evidence.

The '513 patent describes a process for the production of human EPO from human lymphoblastoid cells. Trial Ex. 2374 at 1:21-26. More precisely, Sugimoto teaches that if a human cell line that produces EPO is fused with a human lymphoblastoid cell line, the resulting fused cells produce significant amounts of EPO. Trial Tr. at 1226:21 to 1227:7, 1797:10-19. Sugimoto also advises that (1) conventional techniques can be utilized to achieve purification; and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Trial Ex. 2374 at 3:51 to 4:2. During the *Markman* hearing, counsel for Amgen admitted that its patent covered subject matter that included Sugimoto's work, but counsel also explained that Amgen distinguished Sugimoto during prosecution on the basis that Sugimoto "didn't succeed in actually making a cell that was capable of producing EPO." Tr. of *Markman* Hr'g, Vol. III at 50:1-7. Not surprisingly then, Amgen countered TKT's contention that Sugimoto anticipated Amgen's invention by arguing that Sugimoto was not enabled.

Amgen's contention was supported by trial testimony. On cross examination, Dr. Erslev agreed that the Sugimoto process was "very complex" and that he was "flabbergasted" when he first read Sugimoto's procedure. Trial Tr. at 1754:24 to 1755:9. According to Dr. Erslev, no one had attempted to use Sugimoto's process to produce erythropoietin prior to 1984 despite significant financial incentives to do so. *See id.* at 1755:10-12. Furthermore, according to Dr. Erslev, no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure. *Id.*

at 1755:17 to 1756:3. In light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race.

To counter, TKT proffered its Vice President of Molecular Biology, Dr. Michael Heartlein, who testified regarding experiments he performed in which he fused a lymphoblastoid cell with a human cell producing EPO and studied the results of these fused, or hybrid cells. *Id.* at 1791:12-20, 1795:13-17. In addition to using TKT's EPO-producing HT1080 cells, Dr. Heartlein selected two types of liver carcinoma cells as his EPO producing cells, HepG2 and Hep3B cells. *Id.* at 1798:12-21. In the presence of polyethylene glycol ("PEG"), which causes the destablilization of the cell membranes, the contents of the two cells were mixed together. Once PEG is removed, the membranes resealed, forming the fused or hybrid cells. *Id.* at 1799:17-22. After fusing the cells, Dr. Heartlein cloned out individual cell lines from the pool of fused cells, *see id.* at 1800:11-13, and then quantified the EPO in each of these clones using a commercially available EPO immunoassay, *see id.* at 1801:14-18. He found approximately a six-fold increase in EPO production rates in the cloned cells compared to that of the parental EPO producing cells. *Id.* at 1802:6-7, 1803:15-17. Thus, Dr. Heartlein concluded that he was "able to isolate hybrid cells between a lymphoblastoid cell and a human cell producing EPO, and . . . found that the majority of the clones that were isolated were producing more EPO than the original . . . human cell producing EPO." *Id.* at 1796:12-16. His testimony was intended to show that Sugimoto's process could be performed with routine experimentation and would produce results similar to those reported by Sugimoto. Yet Dr. Heartlein's procedures suffer from a series of deficiencies.

First, Dr. Heartlein could not identify any clones producing EPO in fusions involving the HepG2 cells. *Id.* at 1803:18 to 1804:3, 1829:19-21. Because Sugimoto's patent is not limited to certain types of EPO-producing cells, Trial Ex. 2374 at 6:64-65 (describing "human cells capable of producing human erythropoietin"), the failure to produce EPO from a lymphoblastoid/HepG2 hybrid cell alone indicates that Sugimoto's patent is not enabled. *Genentech, Inc.* v. *Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). In fact, the only fused cells that were successful in producing EPO were those that were produced with HT1080 cells that had been altered by the addition of a nonhuman promoter. Trial Tr. at 1830:1-4. These cells, however, were not available in 1983. *Id.* at 1831:9-11.

Second, Dr. Heartlein's process diverged in a number of ways from that taught by Sugimoto. Whereas Sugimoto's patent only addresses growing up his lymphoblastoid cells in vivo, Dr. Heartlein used only in vitro processes. *Id.* at 1809:14 to 1810:5. Additionally, unlike the EPO-producing cells utilized by Dr. Heartlein, Sugimoto actually used and disclosed minced human kidney tumor cells. *Id.* at 1812:10 to 1813:3. Though he searched, Dr. Heartlein was unable to obtain such cells. *Id.* at 1813:4-13. Dr. Heartlein was also unable to obtain any of the lymphoblastoid cells that are identified in the patent. *Id.* at 1816:2-14. Because he could not obtain the same starting materials as Sugimoto, Dr. Heartlein could not directly repeat any of Sugimoto's examples. *Id.* at 1819:18-23. Thus, TKT provided no evidence adequate to overcome the presumption that the Patent Office correctly rejected the contention that Sugimoto was an anticipating reference. TKT's evidence merely confirms that rejection. Consequently, TKT has failed to show by clear and convincing evidence that Sugimoto's '513 patent anticipated the Amgen patent.

Furthermore, none of the cited references disclose each and every limitation of any of Amgen's individual claims. *Helifix*, 208 F.3d at 1346. As to Claim 1 of the '422 patent, none of the cited references describe a therapeutically effective amount of EPO or the purification of human EPO from mammalian cells grown in culture. Additionally, all but two of the sources (Sugimoto's patent and Tajima's patent application) fail to mention the potential use of EPO generated from hybrid cells in a pharmaceutical composition. Because these references do not describe each claim limitation of Claim 1 of the '422 patent, they do not anticipate that claim.

Similarly, none of the references anticipate the '349 patent. Independent Claims 1 and 4 of the '349 patent are not anticipated by any of these references because none of them disclose the use of non-human DNA sequences that control transcription. Furthermore, other than Sugimoto's patent, none of the references describe the cells as capable of producing in the medium of their growth in excess of 100 units of EPO per 10^6 cells. In addition, neither the Toyama et al. nor Sugimoto references discuss in vitro propagation of their hybrid cells. Because these references fail to disclose essential elements of the relevant claims, they do not anticipate the '349 claims.

Likewise, none of the references anticipate the '933 patent. Because these references fail to address glycosylation of the EPO glycoproteins produced from their hybrid cells, they simply do not describe (1) any differences in glycosylation between their proteins and urinary EPO proteins, as required by Claim 1 of the '933 patent; or (2) any molecular weight comparisons with human urinary EPO as required by Claim 2 of the same patent. In addition, all of the references fail to examine the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. Thus, because the references do not disclose each and every limitation of the '933 claims, they do not anticipate the '933 patent.

The same conclusion arises with respect to the '080 patent. Each asserted claim makes reference to the mature erythropoietin amino acid sequence of Figure 6 which, of course, is unique to the Amgen patent. In fact, as Dr. Lodish explained, the sequence disclosed in Figure 6 is at the heart of Amgen's invention. None of the cited references discuss in any way the amino acid sequence of human erythropoietin. Moreover, as previously mentioned with respect to the '933 claims, all of the references fail to examine the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, which is a limitation contained in all three asserted claims of the '080 patent. Thus, because none of these references disclose each element of any specific asserted claim in this litigation, these references do not anticipate any of Amgen's claims.

b. *Prior Administration of Raw Plasma*

TKT also failed to show by clear and convincing evidence that Dr. U. Essers' raw plasma preparation references meet each and every limitation of Amgen's claims.[26] *See* Trial Exs. 2415-17. The three references report experiments performed by Dr. Essers whereby a small group of both anemic and healthy patients received infusions of erythropoietin-rich plasma. *See id.* Dr. Essers had to use raw human plasma because, at the time she performed her work, there was no erythropoietin available in the quantity and purity required for therapeutic use. Trial Tr. at 1709:4-10. Dr. Essers reported

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[26] These are the three references: U. Essers et al., *Effect of Erythropoietin in Normal Men and in Patients with Renal Insufficiency*, 11 European Dialysis & Transplant Ass'n Proc., Biomed W1 EU715, 398-402 (1975) (Trial Ex. 2417); U. Essers et al., *Weitere Untersuchungen zur Wirksamkeit von Erythropoietin bei Patienten mit Niereninsuffizienz*, 99 Deutsche Medizinische Wochenschrift, 1618-24 (1974) (Trial Ex. 2415); U. Essers et al., *Zur Wirkung von Erythropoietin bei Gesunden und bei Patienten mit chronischer Uramie*, 51 Klinische Wochenschrif 1005-09 (1973) (Trial Ex. 2416).

that many of the patients showed an increase in their reticulocyte counts. *See* Trial Exs. 241517; Trial Tr. at 1555:20 to 1556:7. Yet despite this increase in the reticulocytes, Dr. Essers saw no improvement in the more meaningful measurement of hematocrit or hemoglobin levels of her patients. *See* Trial Ex. 2415; Trial Tr. at 1710:21-25, 1712:7 to 1713:13. In the "Open Discussion" portion of the document published after the European Dialysis and Transplant Association Proceedings, Dr. Essers participated in the following exchange:

> LEBER You have demonstrated that after erythropoietin infusion reticulocytes increased in uraemic patients. Was this accompanied or followed by an increased haemoglobin haematocrit value, and erythrocyte count as well. Or was it only an increase in the reticulocyte count?
>
> ESSERS There was only an increase in the absolute reticulocyte count. I think this was due to the fact that we did not have enough erythropoietin to give the patient to stimulate an increase in haemoglobin.

Trial Ex. 2417 at 401-02. Dr. Essers never proved that anemia could be corrected using her raw plasma preparation. Trial Tr. at 1714:21-23. Thus, while Dr. Essers may have been successful in elevating the reticulocyte counts of some of her patients, the failure to initiate and sustain an increase in the hematocrit or hemoglobin levels reveals that the Essers' work did not meet Amgen's therapeutic effectiveness standard. *See* Trial Ex. 2 at 39:1-4, Trial Ex. 3 at 38:51-53, Trial Ex. 6 at 38:36-41 (pharmaceutical composition claims of '933, '080, and '422 patents, respectively). As a result, Dr. Essers' references do not anticipate the pharmaceutical composition claims.

The references fail to meet other limitations of Amgen's various claims as well. Because the raw plasma was drawn from human blood, Trial Exs. 2415-17, Dr. Essers' EPO product could not be said to be non-naturally occurring, as is

required by Claim 1 of the '933 patent, Trial Ex. 2 at 36:17, and Claim 3 of the '080 patent, Trial Ex. 3 at 38:45. In addition, because the EPO glycoprotein is not isolated from the plasma preparation, the Essers' preparation does not satisfy the first limitation of Claim 2 of the '080 patent. *See id.* Trial Ex. 3 at 38:39-44. Moreover, like the tumor cell references, Dr. Essers' articles do not address glycosylation or molecular weight differences and, therefore, do not anticipate either Claim 1 or Claim 2 of the '933 patent. *See* Trial Ex. 2 at 38:17-24. With respect to the '422 patent, in addition to its failure to provide a therapeutically effective amount of human erythropoietin, Dr. Essers' plasma preparation is not purified from mammalian cells grown in culture, as it is drawn from human blood. Trial Ex. 6 at 38:37-41. Thus, the references regarding Dr. Essers' plasma preparation work fail to anticipate any of the claims asserted by Amgen.

c. *Prior Administration of Urinary EPO*

In support of its anticipation defense, TKT also relies upon a clinical study performed under the direction of Dr. Eugene Goldwasser. As an initial matter, Amgen again challenges whether this study constitutes prior art under 35 U.S.C. § 102. For the same reasons that the Court rejected Amgen's attack on the 1985 Saito et al. and 1986 Sherwood and Shouval experiments, the Court rebuffs this attack as well. Because the documents submitted as exhibits in this case reveal that Dr. Goldwasser began this clinical study in 1979-1980 at the University of Chicago in Illinois, *see* Trial Ex. 2055, it could fairly be said that it predates Amgen's patent application. *See* 35 U.S.C. § 102(a), (g). That it appears to be prior art is only part of the analysis, for the only prior art that renders Amgen's claims invalid is that which anticipates Amgen's claims. In order to make that determination, one must understand what it is Dr. Goldwasser accomplished.

Dr. Goldwasser obtained a preparation of highly purified erythropoietin derived from human urine. Trial Ex. 2055. Then, in the clinical study, approximately 10,000 units (in dosages of 500 and 1000 units) of human urinary EPO was administered to three anemic patients. Trial Ex. 2057 at 19; *see also* Trial Tr. at 1579:5-9. Dr. Goldwasser observed a number of biologic effects in the patients. He reported an increase in reticulocyte count in all three patients, an increase in erythroid cells in the marrow and an increased plasma iron clearance rate in two patients, and an increase in red cell mass in one patient. *See* Trial Ex. 2057 at 19. Testifying about Dr. Goldwasser's work, Dr. Erslev explained that these "results . . . indicate very strongly that the patients did respond by having an increase in the rate of red cell production." Trial Tr. at 1578:4-6. According to Dr. Erslev, the increase in (1) the reticulocytes; (2) the plasma iron clearance rate; and (3) the red blood cell mass are all "strong evidence for an increase in the rate of red cell production." *Id.* at 1578:10-12; *see id.* at 1578:7 to 1579:2. Dr. Erslev also conceded that an increase in reticulocytes alone does not correct a patient's anemia. *Id.* at 1688:14 to 1689:4.

Importantly, however, Dr. Goldwasser admits that "[t]here was no significant change in hematocrit in any patient," Trial Ex. 2057 at 19, and Dr. Erslev agreed that the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit, *see* Trial Tr. at 1675:12-23. Due to this lack of effect upon hematocrit levels, the patients did not appear to receive any health benefits from the reported biologic effects. *See id.* at 1719:7-21, 1720:11-13, 1919:4-12. Furthermore, Dr. Goldwasser himself has testified that his abortive, three-patient trial was a failure. *See* Goldwasser Dep. at 317:14 to 321:2. Consequently, the Goldwasser study could not anticipate any of Amgen's claims requiring a therapeutically effective amount of EPO. As the Federal Circuit explained in *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549 (Fed. Cir. 1985), "another's experiment, imperfect and never perfected

will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it." *Id.* at 1558 (quoting *Picard* v. *United Aircraft Corp.*, 128 F.2d 632, 635 [2d. Cir. 1942]). Such is the case here.

In order to refute Dr. Goldwasser's downplaying of his own work, TKT points to statements made by him and Dr. Baron, the researcher working on the project under Dr. Goldwasser's direction, which were made shortly after the experiments. Dr. Baron reported to the FDA that "[d]efinite evidence of erythroid marrow stimulation was detected." Trial Ex. 2058 at 2. Dr. Goldwasser also explained in his National Institute of Health grant application that EPO "can have a physiological effect in this type of anemia." Trial Ex. 2057 at 19. First, these statements do not contradict the conclusion that the clinical study was limited, in the sense that only three patients participated, and abortive, in the sense that sufficient amounts of urinary EPO material was not readily accessible to continue it. Second, while urinary EPO may have had some "physiological effects" including "erythroid marrow stimulation," such effects serve as only evidence of the stimulation of red blood cell production. Such evidence should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged.[27] Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness, Dr. Goldwasser's study, which

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[27] Failure to increase hematocrit levels may have been caused by the fact that the potency of Goldwasser's urinary EPO was less than half that of recombinant EPO. *See* Trial Ex. 137 at 699; Trial Tr. at 1742:3-23. Likewise, the failure to stimulate the production of mature red blood cells may have been caused by the fact that, compared to recombinant EPO, Goldwasser's uEPO cleared from circulation rapidly. *See* Trial Ex. 2058 at 1; Trial Tr. at 1097:8-14, 1102:5-22, 1741:10-12. Regardless of the reason, it is clear that Goldwasser's work did not effect a change in hematocrit. Trial Ex. 2058 at 2 (reporting that no increase in hematocrit level was observed).

revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO. Thus, the study does not anticipate the pharmaceutical composition claims of the '933, '080, and '422 patents. Likewise, because Goldwasser's work failed to stimulate production of red blood cells as well as reticulocytes, the study does not anticipate Claim 1 of the '933 patent and Claims 2 and 3 of the '080 patent.

Furthermore, the Goldwasser study fails to address many of the additional aspects of Amgen's claims. For example, Amgen specifically excluded urinary EPO preparations from the scope of the claims by including the claim limitation "non-naturally occurring" and "not isolated from human urine." Trial Ex. 2 at 38:17; Trial Ex. 3 at 38:44. The purification of EPO from patients with anemia, whose urine often has a high volume of EPO, constitutes an example of naturally-occurring EPO. Thus, Claims 1 and 2 of the '933 patent and Claims 2 and 3 of the '080 patent simply do not encompass Dr. Goldwasser's urinary EPO treatment. *See* Trial Ex. 2 at 3:17-25; Trial Ex. 3 at 38:39-50. Likewise, because Dr. Goldwasser's work does not pertain to cells that have been altered by recombinant means in order to express high levels f EPO, it does not implicate any of the claims of the '349 patent. Trial Ex. 5 at 38:7-14, 18-27, 31-37. Because Dr. Goldwasser's work cannot satisfy these claim limitations, it cannot anticipate Amgen's claims.

2. *Obviousness*

A patent is invalid if the differences between the patented subject matter and the prior art are such that the patented subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a). Whether an invention is obvious is a legal conclusion based upon underlying factual inquiries. *See Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966). As in all other invalidity analyses, the party asserting an obvious-

ness defense must prove the disputed facts by clear and convincing evidence. *See Ga.-Pac. Corp.* v. *United States Gypsum Co.*, 195 F.3d 1322, 1330 (Fed. Cir. 2000).

"Obviousness rests on several critical factual underpinnings: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of skill in the art; and (4) the objective indicia of nonobviousness." *Yamanouchi Pharm. Co., Ltd.* v. *Danbury Pharm., Inc.*, 231 F.3d 1339, 1342 (Fed. Cir. 2000); *see also Graham*, 383 U.S. at 17-18. Among the relevant objective, secondary considerations are: (1) copying; (2) long-felt, but unresolved need; (3) the failure of others; (4) commercial success; (5) unexpected results created by the claimed inventions; (6) unexpected properties of the claimed inventions; (7) licenses revealing industry respect for the invention; and (8) skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Although secondary considerations must be weighed, they do not control the determination of obviousness. *See Richardson-Vicks, Inc.* v. *Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) ("Evidence of secondary considerations [is] but a part of the 'totality of the evidence' that is used to reach the ultimate conclusion of obviousness.").

Unlike the defense of anticipation, which requires a *single* prior art reference to contain each and every limitation of the claimed invention, the defense of obviousness may be made out where it would be obvious to one of ordinary skill in the art to *combine* the teachings of more than one prior art source in order to accomplish the claimed invention. The Federal Circuit, however, has made clear that the elements of this "combination theory" require "a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential evidentiary component of an obviousness hold-

ing.'"[28] *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (quoting *C.R. Bard, Inc.* v. *M3 Sys. Inc.*, 157 F.3d 1340, 1352 [Fed. Cir. 1998]). Such "evidence may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." *Id.* (citing *Pro-Mold & Tool Co.* v. *Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 [Fed. Cir. 1996]). The Federal Circuit has made clear that the showing must be by clear and convincing evidence. Specifically, the showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are insufficient. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Furthermore, the alleged infringer must show that one of ordinary skill in the art would reasonably expect that combining the teachings of myriad sources would achieve success. *Yamanouchi*, 231 F.3d at 341 (citing *In re Longi*, 759 F.2d 887, 896 [Fed. Cir. 1985]); *Ortho Pharm. Corp.* v. *Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992).

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[28] The Federal Circuit has recently reiterated the importance of the motivation to combine requirement:

> As this court has stated, "virtually all [inventions] are combinations of old elements." Therefore, an [accused infringer] may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an [accused infringer] to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> . . . .
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In re Rouffet, 149 F.3d at 1357-58 (internal citations omitted).

TKT first argued that the Sugimoto patent rendered a number of Amgen's claims invalid due to obviousness. A prior art reference must be enabling, however, which thereby places the claimed invention in the possession of the public. *See Akzo N.V.* v. *United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986). In addressing the defense of anticipation, the Court found that the Sugimoto patent was not enabled and, therefore, that it had no effect upon the validity of Amgen's patents. *Supra* Section IV.D.1.a, at 84-89. Because TKT failed to prove that Sugimoto was enabled,[29] Sugimoto is not prior art, and therefore it cannot support TKT's obviousness defense.

Second, TKT relied upon Dr. Goldwasser's urinary EPO preparation as a potential base from which to launch an obviousness sortie. Because Dr. Goldwasser's study was a failure, *see* Goldwasser Dep. at 317:14 to 321:2, the Court already concluded that Dr. Goldwasser's work did not constitute prior art, *supra* Section IV.D.1.c, at 94-98. In addition, particularly where the lead scientist implicitly revealed his disappointment by aborting the work, it seems clear that a person of ordinary skill in the art would not reasonably have expected that Dr. Goldwasser's work would eventually bear fruit. Instead, the more reasonable conclusion would be that

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[29] Had the Court concluded otherwise, however, the Sugimoto patent would go a long way toward proving TKT's obviousness defense. As explained above, Sugimoto disclosed EPO-producing fused cells and advised that (1) conventional techniques can be utilized to achieve purification and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Trial Ex. 2374 at 3:51 to 4:2. Thus, the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. Provided that one of ordinary skill in the art could actually make the EPO-producing cells described in the Sugimoto patent, a point on which TKT failed to persuade this Court, such a combination of prior art materials might render invalid the pharmaceutical composition claims of the '933, '080, and '422 patents.

a urinary EPO preparation would remain unsuccessful in treating anemia despite its stimulation of some preliminary biologic effects.

As against the claims of the '349 patent, TKT points to the various EPO-producing human tumor cell references identified above, *see supra* note 24. Yet all of these references fail to render obvious any of the '349 claims because of one important distinction. The two independent claims of the '349 patent describe cells comprising (1) "non-human DNA sequences that control transcription of DNA encoding human erythropoietin"; or (2) "transcription control DNA sequences, other than human erythropoietin transcription control sequences." Trial Ex. 5 at 38:13-14, 22-23. The references do not describe cells comprising these DNA elements, nor could one of ordinary skill in the art make the cells claimed in the '349 patent with the knowledge provided by the tumor cell references. The key knowledge that the art lacked prior to Amgen's disclosure was EPO's genetic sequence. Without identifying the sequence of the DNA encoding human erythropoietin, one of ordinary skill in the art would be unable to hook up transcription control sequences in a way that caused transcription of the EPO gene. The cells claimed in the '349 patent are distinct not only because of the high volume of EPO they are capable of producing, but also because of the cells' unique genetic makeup. The tumor cell references do not speak to these genetic characteristics nor would any knowledge possessed by those of ordinary skill in the art in 1983-1984 fill this gap. Moreover, there is no clear evidence that these prior art tumor cells produced EPO in the medium of their growth in excess of 100 or 1000 U of erythropoietin per 10^6 cells in forty-eight hours. While producing EPO in such abundance was indeed one of the primary goals of researchers at that time, that goal continued to escape their grasp. Even with knowledge of these prior art cells, those of ordinary skill at that time simply did not have the ability to induce greater EPO production from these cells

or from other sources of EPO for that matter. Thus, having cells that showed some EPO production was a far cry from having cells that produced EPO to the degree claimed in the '349 patent. Consequently, the Court finds that TKT has failed to show by clear and convincing evidence that the tumor cell references render the '349 claims obvious.

Third, TKT contended that the human tumor cell references could be combined with the work of Drs. Essers or Goldwasser as well as the purification work of Yanagawa or Chiba to defeat the validity of Amgen's pharmaceutical composition claims. *See* Trial Exs. 2055-56, 2058, 2231, 2252, 2415-17. A number of the tumor cell references and the Yanagawa reference were explicitly disclosed by Amgen during the patent prosecution. Trial Ex. 1 at 7:63 to 8:15. The Court infers that the Patent Office, therefore, contemplated this question and decided in favor of nonobviousness. Importantly, TKT failed to prove the existence of any suggestion in the prior art to combine these references so as to produce the pharmaceutical compositions claimed in the '933, '080, and '422 patents. Furthermore, the Court is not persuaded that one of ordinary skill in the art could have used the Yanagawa or Chiba purification methods to purify to substantial homogeneity the EPO produced in the tumor cell cultures. Likewise, the evidence was insufficient to warrant the conclusion that plasma EPO could be purified to homogeneity. The fact that no one has ever—then or now—attempted to determine if a pharmaceutical composition comprising human EPO could be made from these cultured prior art cells also informs the Court's decision. Trial Tr. at 1750:23 to 1751:14, 1753:17 25; 1755:10 to 1756:3. In light of all these facts, the contention that these various references could be combined to produce a pharmaceutical composition meeting the limitations of Claim 9 of the '933 patent, Claim 4 of the '080 patent, and Claim 1 of the '422 patent is simply unsubstantiated conjecture.

Finally, the secondary considerations in this case are telling. *See Pall Corp.* v. *Micron Separations, Inc.*, 792 F. Supp. 1298, 1316 (D. Mass. 1992) ("Objective evidence of non-obviousness may well be the most pertinent probative and revealing evidence available to aid in reaching a conclusion with respect to [the] issue [of obviousness.]") (citations omitted), *aff'd in part, rev'd in part*, 66 F.3d 1211 (Fed. Cir. 1995); *see also Richardson*, 122 F.3d at 1483. Dr. Erslev testified at length about the repeated failures of researchers around the world who were attempting to create an EPO product effective in treating patients with anemia. *See, e.g.*, Trial Tr. at 1650:8 to 1651:12, 1657:4-13, 1657:19 to 1658:3, 1658:12 to 1659:1, 1709:410, 1710:15-20, 1712:7 to 1714:20, 1715:15 to 1716:25. Throughout the 1970s, researchers sought to conduct clinical studies with EPO to determine its therapeutic effectiveness, but such trials were hampered by a lack of supply of EPO from natural sources. *Id.* at 1651:22 to 1652:18. Thus, Dr. Erslev explained that the need for the mass production of EPO had existed for "many, many, many years." *Id.* at 1673:14-21. Additionally, in light of the complications associated with the then existing forms of treatment for the anemia of chronic renal failure, there was a need for an alternative therapy. *Id.* at 1669:6 to 1670:13. Indeed, until the advent of Amgen's recombinant EPO product, the anemia associated with chronic renal failure remained uncorrected. *See id.* at 1659:2 to 1666:25, 1667:15 to 1668:10, 1669:1-5, 1720:14-17. The results of the first clinical trials with recombinant human EPO were "dramatic beyond anyone's dreams." *Id.* at 1665:10 to 1667:4. Before the advent of Amgen's product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known. *Id.* at 1579:22 to 1580:19, 1656:11-18, 1669:1-9, 1720:11-17. Furthermore, Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world. *Id.* at 1671:16 to

1673:3. As a result, Dr. Lin received widespread public acclaim for his work. Trial Exs. 156-58; Trial Tr. at 981:17 to 982:6, 984:8 to 985:10.

From these uncontested factual conclusions, it is but a short hop to infer that, prior to Amgen's pathbreaking invention, there was a long-felt need for a human EPO preparation that was therapeutically effective in treating the anemia of chronic renal failure. Despite researchers all across the globe seeking to fulfill that need (and commercial entities desperately hoping to capitalize on it), Amgen was the first to succeed. Amgen's invention opened the floodgates for EPO production and ultimately led to a therapeutically effective pharmaceutical composition containing human EPO. One cannot help but wonder if achieving such an outcome by combining certain known prior art techniques were truly obvious to those of ordinary skill in the art, why didn't one of the myriad competitors do it? Consequently, the Court finds that the secondary considerations strongly counsel the Court against a finding of obviousness.

Thus, having considered the scope and content of various prior art references, the differences between such references and the claimed inventions, how one skilled in the art might combine such references in order to make what was claimed by Amgen, and the objective, secondary considerations, the Court concluded that TKT failed to persuade the Court by clear and convincing evidence that Amgen's inventions were obvious in light of prior art. As a result, pursuant to Rule 52(c), the Court granted judgment of validity with respect to the defense of obviousness.[30] *See* Trial Tr. at 2534:7-10. The

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[30] The Court's ruling had one exception, however. Trial Tr. at 2534:7-22. The Court permitted TKT to present additional evidence with respect to whether the examiner was unaware of material information that may have colored the examiner's view of the relationship between the prior art and Amgen's claimed inventions. *Id.* at 2534:10-18. In light of the Court's findings with respect to TKT's inequitable conduct defense, *see infra*

Court declined to make any further rulings regarding TKT's validity defenses.

Following the Court's Rule 52(c) prior art determinations, the Court undertook to receive Amgen's rebuttal evidence regarding TKT's validity defenses and also received testimony, offered by TKT, from attorneys involved in the prosecution of Amgen's patents. When all the evidence had been received, the Court entertained closing arguments and took the remaining issues under advisement. Beginning with the question of infringement, the latter portion of this memorandum resolves these issues.

E. *Infringement*

Proof of infringement may be made out pursuant to either of two theories: literal infringement or the doctrine of equivalents. In determining whether an accused product literally infringes a patent claim, the Court applies a two-step analysis. *CAE Screenplates, Inc.* v. *Heinrich Fiedler GMBH & Co. KG*, 224 F.3d 1308, 1316 (Fed. Cir. 2000). First, the claims must be construed to determine the scope of the claims. *Id.*; *see also Kahn* v. *Gen. Motors Corp.*, 135 F.3d 1472, 1476 (Fed. Cir. 1998). Second, the claims must be compared to the accused product. *CAE Screenplates*, 224 F.3d at 1316; *Kahn*, 135 F.3d at 1476. If the accused product meets each of the limitations contained in a claim, then the product literally infringes that claim. If, however, even one limitation is not met, then the product does not literally infringe. A plaintiff in the latter circumstance is not without a remedy and, therefore, the defendant is not yet out of the woods. "A device which does not infringe a patent claim literally may still infringe the claim under the doctrine of equivalents if each and every

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Section IV.F.1, at 166-94, the Court holds that TKT's evidence adds nothing to its prior art defense. Consequently, the Court rejects in toto TKT's claim that Amgen's inventions were either anticipated by or obvious in light of prior art sources.

limitation of the claim is literally or equivalently present." *CAE Screenplates*, 224 F.3d at 1318-19 (citing *Pennwalt Corp.* v. *Durand-Wayland, Inc.*, 833 F.2d 931, 934-35 [Fed. Cir. 1987]). A claim limitation is equivalently present in an accused product if there are only "insubstantial differences" between the limitation and the corresponding aspects of the product. *Hilton Davis Chem. Co.* v. *Warner-Jenkinson Co.*, 62 F.3d 1512, 1517-18 (Fed. Cir. 1995), *rev'd on other grounds*, 520 U.S. 17 (1997). "The usual test of the substantiality of the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element." *Upjohn Co.* v. *Mova Pharm. Corp.*, 225 F.3d 1306, 1309 (Fed. Cir. 2000); *see also Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950). "The application of infringement by equivalents, however, is limited by the doctrine of prosecution history estoppel." *CAE Screenplates*, 224 F.3d at 1319; *see also Festo Corp.* v. *Shoketso Kinzoku Kogyo Kabushiki Co., Ltd.*, No. 95-1066, 2000 WL 1753646, at *3 (Fed. Cir. Nov. 29, 2000). Prosecution history estoppel "provides that a patent owner can be estopped from relying upon the doctrine of equivalents when the patent applicant relinquishes coverage of subject matter during the prosecution of the patent, either by amendment or argument." *CAE Screenplates*, 224 F.3d at 1319; *Pharmacia & Upjohn Co.* v. *Mylan Pharms., Inc.*, 170 F.3d 1373, 1376-77 (Fed. Cir. 1999). With this legal framework in mind and having already construed a number of key terms, the Court turns its face "to the stormy seas [of infringement] and bids the land farewell." Tommy Makem, *Ballad of the Lady Jane*, *on* Lonesome Waters (Shanachie Records Co. 1993).

1. *The '349 Patent*

As matter of fact, the Court finds that TKT's R223 cells meet each of the limitations of Claims 1, 3, 4, and 6 of the

'349 patent. A number of subsidiary factual findings relevant to this patent have already been made on the summary judgment record. First, the Court ruled on March 28, 2000 that R223 cells are vertebrate cells. Tr. of *Markman* Hr'g, Vol. II at 136:3-4. The admission by TKT's counsel during the *Markman* hearing that R223 cells are vertebrate cells under the Court's construction, i.e. cells from an animal having a backbone, is sufficient to warrant a factual finding in that regard. *Id.* at 131:5-6. Second, TKT's Rule 30(b)(6) designee, David S. Johnson, testified at his deposition that R223 cells are vertebrate cells. Galvin Decl. (Nov. 4, 1999) Ex. 4 at 76:12-14. In short, the R223 cell line is derived from the HT1080 cell line which is, in turn, derived from a cancerous human cell. Thus, the cell is from an animal having a backbone—a human. Trial testimony by Dr. Kingston during Amgen's cross examination—though unnecessary in light of the summary judgment determination—bolsters this finding. Trial Tr. at 1380:25 to 1381:16. Third, the Court ruled that R223 cells are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 units of erythropoietin per 10^6 cells in forty-eight hours as determined by radioimmunoassay ("RIA").[31] Dr. Ronald W. McLawhon's second declaration was very influential in this determination. In particular, after performing RIAs with TKT's R223 cells, which yielded erythropoietin in amounts far in excess of 100 units per 10^6 cells in forty-eight hours, Dr. McLawhon concluded that R223 cells were capable of producing more than 1000 units of human erythropoietin per 10^6 cells in forty-eight hours. *See* McLawhon Decl. (Mar. 3, 2000) at 8, ¶ 23. TKT produced no evidence refuting the implications of Dr. McLawhon's RIA tests. Again, though such evidence is unnecessary

[31] RIA is a widely used technique for quantifying the amount of a protein in a sample. Binding of an antibody to the protein of interest allows for the identification of that protein.

in light of the Court's summary judgment determination, substantial evidence introduced at trial supports this ruling. *See* Trial Ex. 14 at HMR 336545; Trial Ex. 19 at IND000568; Trial Tr. at 277:7 to 279:5, 1473:12-25. Fourth, the Court ruled on the summary judgment record that the R223 cell line contains non-human DNA sequences that control transcription. The R223 cells contain the cytomegalovirus ("CMV") promoter, a viral (and therefore, nonhuman) DNA sequence that initiates transcription. Galvin Decl. (Nov. 4, 1999) Ex. 4 at 98:11-14, 129:23 to 130:13, 134:3-25. The CMV promoter is not derived from the human genome. *Id.* Ex. 3 at 37:21-22. This CMV promoter is present in R223 cells and initiates the transcription of sequences that encode human erythropoietin. *Id.* Ex. 5 at 438:19 to 439:2, 480:3-13. Finally, the IND displays a schematic diagram of the vector used by TKT, known as the targeting construct pREPO22, which depicts the CMV promoter "used for initiation f the GA-EPO mRNA transcript . . ." *Id.* Ex. 12 at IND000788. In light of the evidence presented by Amgen and not refuted by TKT, the Court ruled on summary judgment that the R223 cell line contains nonhuman DNA sequences that control transcription. Upon further reflection, however, the Court modifies its summary judgment determination. The evidence on the summary judgment record was sufficient to show that the CMV promoter *initiates* transcription, but upon reflection was insufficient to prove that the CMV sequence also *regulates* transcription. Under the Court's construction, both actions are necessary in order to "control" transcription. Neither party has been prejudiced by this modification for, as is seen below, this issue was the subject of much testimony during trial.

As to the remaining limitations in Claim 1 of the '349 patent, the Court ruled that a trial was necessary in order to determine whether the R223 cells literally infringe. After hearing evidence on these matters, the Court now finds as matter of fact that the R223 cells meet the remaining limitations in Claim 1. First, the R223 cells can be propagated

in vitro. Joint Pretrial Mem. at 5, ¶ 23. Second, R223 cells contain a DNA sequence that not only initiates transcription, but also regulates transcription of DNA encoding human erythropoietin. In particular, the R223 cells contain CMV enhancer sequences that regulate transcription of DNA encoding human erythropoietin by determining the rate at which RNA polymerase binds and makes an RNA copy of the DNA encoding human EPO. *See* Trial Ex. 19 at IND000559, Trial Ex. 20 at IND000829-30. As Dr. Harvey Lodish explained, a regulatory DNA sequence called an enhancer not only binds proteins that interact physically with RNA polymerase, but also increase the ability of RNA polymerase to bind to the promoter sequence. Trial Tr. at 106:11 to 107:2. Thus, "a strong enhancer would be one which would initiate or cause RNA polymerase to initiate transcription at a very high rate." *Id.* at 107:3-5. Dr. Lodish subsequently testified that TKT's CMV sequence contains several strong enhancers that are capable of binding proteins that determine the frequency or rate of transcription initiation of DNA encoding human EPO. *Id.* at 271:11-17. Dr. Lodish firmly based his opinion not only on his review of the relevant literature, but also on TKT's own IND submissions. *Id.* at 271:11 to 276:10. Similarly, Dr. Robert E. Kingston admitted on cross-examination that the R223 cells contain CMV enhancer sequences. *Id.* at 1384:2-3. He agreed that the CMV enhancer sequences are capable of attracting or binding certain proteins that can affect the rate or frequency of transcription initiation. *Id.* at 1393:16-22. Dr. Kingston also agreed that the CMV enhancer sequences are positioned in the R223 cells at a location so as to affect the rate or frequency at which RNA transcripts that include the EPO DNA are formed. *See id.* at 1393:23 to 1394:9. As a result, the Court now finds that the CMV enhancer DNA sequences regulate transcription of DNA encoding human EPO. Thus, in conjunction with its summary judgment ruling that the CMV promoter initiates transcription of EPO DNA, the Court finds that the R223

cells contain non-human DNA sequences that control transcription of DNA encoding human erythropoietin.

Thus, the Court finds as matter of fact that TKT's R223 cells (1) are vertebrate cells that can be propagated in vitro; (2) are capable, upon growth in culture, of producing erythropoietin in the medium of their growth in excess of 100 units of erythropoietin per 10^6 cells in forty-eight hours as determined by RIA; and (3) contain non-human DNA sequences that control transcription of DNA encoding human erythropoietin. Consequently, the defendants' R223 cells literally infringe Claim 1 of the '349 patent.

Dependent Claim 3 of the '349 patent differs from Claim 1 only in that it specifies that the vertebrate cells be capable of producing in excess of 1000 units of EPO per 10^6 cells in forty-eight hours as opposed to the 100 units specified in Claim 1. Trial Ex. 5 at 38:18-20. The trial evidence on this point is somewhat circuitous, for Amgen relies on data obtained from an enzyme-linked immunosorbent assay ("ELISA")[32] as opposed to a RIA. The terms of Claim 3, however, fail to specify the test by which the amount of EPO must be measured. Furthermore, the Court sees no reason why it should incorporate the RIA limitation of Claim 1 into dependent Claim 3. Claim 3's dependence upon Claim 1 requires certain elements of Claim 1 to be satisfied in order to infringe Claim 3. Yet Claim 3 introduces a heightened standard for EPO production that is not limited by the method of measurement. Thus, Claim 3 can be literally infringed upon evidence that the infringing cells produce the required amount of EPO as measured by tests other than RIAs. Nevertheless, even if the Court were to hold that radioimmunoassays were required under Claim 3, Amgen's evidence regarding the comparability of ELISA and RIA measurements would more

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[32] Although similar to RIA, ELISA uses a different method of identifying the protein of interest.

than support the Court's finding of infringement under the doctrine of equivalents. A summary of the relevant evidence follows. First, TKT's IND discloses that the R223 cells are capable of producing 2118 units of EPO per 10^6 cells per day when grown in culture as measured by an ELISA assay. *See* Trial Ex. 19 at IND000568, 000842. Furthermore, the ELISA and RIA assays provide comparable measures of EPO activity because, in each test, the results are normalized to a known amount of EPO. Trial Ex. 14 at HMR 336545; Trial Tr. at 278:17 to 279:5, 1473:12-25. As a result, the R223 cells are capable of producing in excess of 1000 units of EPO per 10^6 cells in forty-eight hours when grown in culture. *See* Trial Ex. 14 at HMR 336545; Trial Ex. 19 at IND000568; Trial Tr. 277:7 to 279:5, 281:12-19, 1473:12-25. Thus, either literally or under the doctrine of equivalents, the Court finds that the R223 cells infringe Claim 3 of the '349 patent.

Claim 4 of the '349 patent differs from Claim 1 in the phraseology describing the transcription control DNA sequences. Whereas Claim 1 specifies vertebrate cells "comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin," Trial Ex. 5 at 38:12-14, Claim 4 claims vertebrate cells "which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin." *Id.* at 38:22-24. Claim 4 actually describes a larger subset of claimed transcription control sequences than Claim 1 because it sweeps within its reach not only all non-human DNA sequences, but also all human DNA sequences other than human EPO transcription control sequences. Despite this distinction in the claim language, the same factual finding results. The CMV DNA sequences in R223 cells are not human erythropoietin control sequences. A CMV is a virus whose DNA material is not naturally found on the human genome. *See* David Johnson Designated Dep. at 98:8-14. The CMV DNA sequences, therefore, are not human. Because the CMV DNA sequences are not human,

they cannot possibly be human erythropoietin transcription control sequences. *See* Trial Ex. 18 at IND000017; Trial Ex. 20 at IND000790. The trial testimony of Dr. Lodish and Dr. Kingston, in addition to the exhibits and testimony referred to regarding Claim 1, *see* Trial Tr. at 282:12 to 283:6, 296:20 to 298:14, 299:21 to 300:5, 1409:4-25, and designated deposition testimony amply supports this finding, *see* David Johnson Designated Dep. at 96:8 to 98:14, 129:5 to 130:7; Treco Designated Dep. at 446:24 to 447:2, 478:9 to 479:14 (explaining that the CMV immediate early gene has transcription control sequences that control transcription of the DNA sequences that encode gene activated erythropoietin). In light of such admissions and the other evidence presented during the course of trial, the Court is persuaded that R223 cells contain transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin. Consequently, the Court finds as matter of fact that TKT's R223 cells literally infringe Claim 4 of the '349 patent.

Claim 6 of the '349 patent depends upon Claim 4, but differs, just as Claim 3 differs from Claim 1, in the amount of units of EPO that the cell is capable of producing. Trial Ex. 5 at 38:31-33. Having already determined both that the R223 cells are capable of producing in excess of 1000 units of EPO per 10^6 cells in forty-eight hours when grown in culture and that the R223 cells meet the other limitations of Claim 4, nothing more need be said. Thus, based on the evidence discussed above underlying the factual findings regarding Claims 3 and 4 of the '349 patent, the Court finds as matter of fact that the R223 cells infringe Claim 6 of the '349 patent.

In determining that the R223 cells infringe Claims 1, 3, 4 and 6 of the '349 patent, the Court necessarily rejected all of TKT's infringement defenses. The most plausible, but ultimately unavailing contentions, are considered here. TKT primarily attempts to distinguish its cells on the basis of the

origin of the human EPO DNA contained therein. Indeed, it is true that Amgen inserts the EPO DNA by transfection into the non-human host cell, whereas TKT's human cell already contains the human EPO DNA. Yet this factual distinction is immaterial because the claim language is not limited by the origin of the EPO DNA. In short, Amgen only had to show and actually showed that the DNA that the non-human transcription control DNA sequences controlled was the DNA encoding human EPO. *See, e.g.*, Trial Tr. 270:4 to 271:6, 276:15 to 277:1, 1393:5 to 1394:9. This is all it needs to show on this point. Whether the DNA encoding human EPO originated within or outside f the host cell simply does not matter.

Even if TKT's distinctions were sufficient to defend against literal infringement, it could not have defended against the doctrine of equivalents given Amgen's proffered evidence. Dr. Lodish explained that because the two distinct cells have the same sequence within the coding region, the origin of the DNA is immaterial, and precisely the same glycoprotein is produced in terms of structure and biological activity.[33] Trial Tr. at 174:18 to 175:18; *see also id.* at 175:1-18, 303:3-15, 1376:15 to 1378:8, 1448:2 to 1451:9 (explaining that the fact that TKT's R223 cells produce EPO from DNA that is endogenous rather than exogenous to the host cell does not alter the structure or the glycosylation of the EPO protein that is ultimately secreted by the R223 cell). Furthermore, TKT admitted to the FDA that its clinical trials show that HMR4396 produced from vertebrate cells con-

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[33] Dr. Kingston's testimony during cross-examination, though more constrained than Dr. Lodish's, supports Dr. Lodish's opinion on this narrow point. On cross-examination, Dr. Kingston testified that "[t]here are nonhuman DNA sequences in [TKT's] cells which work together with human DNA sequences in [TKT's] cells to control transcription." Trial Tr. at 1409:7-9; *see also id.* at 1376:15 to 1377:19, 1448:7 to 1449:10, 1450:11 to 1451:9.

taining endogenous human EPO DNA and EPOGEN® produced from vertebrate cells containing exogenous human EPO DNA are equivalent in their therapeutic properties. Trial Ex. 122 at HMR 801225, 801231, 801281; Trial Ex. 123 at HMR 801510; Trial Tr. at 492:8 to 493:1. A subsequent pharmaceutical manufacturer may argue to the FDA that its product is as safe or as effective as another product already on the market, but it ought not be permitted to run from its earlier representations once the matter of patent infringement comes its way.

The Court also finds that the chromosomal location of the DNA encoding EPO as well as the genomic environment surrounding the EPO DNA is irrelevant to the infringement analysis of the '349 claims, and therefore, TKT's attempts to distinguish its cells on these bases is simply misguided. TKT's evidence in this regard seems to be offered for the purpose of showing that its cells are somehow less engineered (and more natural) than Amgen's. Yet without making any determination regarding whether these distinctions even exist, the Court concludes that nothing in the claim language of the '349 claims calls for these distinctions. As a result, the Court deems both TKT's evidence supporting these contentions and Amgen's rebuttal evidence on these issues (including Dr. Tlsty's flourescent in situ hybridization ["FISH"] analysis data with respect to the R223 cells) immaterial.

Finally, and importantly, the fact that the R223 cells contain the endogenous human EPO promoter and regulatory elements does not matter. The term of art "comprise" or "comprising" as used in Claims 1 and 4 is not meant to indicate that an exhaustive list is following. Instead, it merely means that the object of the phrase—in this case, the cells—contains at least (though not exclusively) the item or items listed thereafter. While the specified elements following "comprise" and "comprising" are essential, additional elements may be added to the specified elements and still form a

construct within the scope of the claim. *Genentech, Inc.* v. *Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997). Thus, it matters not that the endogenous EPO promoter and enhancer sequences are present, as long as the cells contain the non-human (Claim 1) or other than human (Claim 4) EPO promoter sequences. Because the R223 cells do, they infringe Claims 1, 3, 4, and 6 of the '349 patent.

Amgen also contends that TKT infringes Claim 7 of the '349 patent. Unlike the other claims of the '349 patent, Claim 7 is directed to a process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, the claimed vertebrate cells. While the methods employed by TKT to reach the result protected by Amgen's cell product claims are immaterial to the infringement analysis of those cell product claims, such methods are crucial with respect to Claim 7. *See supra* Section IV.C.2, at 66-74 (regarding the judgment of non-infringement of the '698 patent).

In light of this, the Court concludes that Amgen has failed to prove by a preponderance of the evidence that TKT's process for the production of erythropoietin infringes Claim 7. As described in more detail with respect to the ruling of non-infringement of the '698 patent, *see supra* Section IV.C.2, at 6874, TKT's process for producing erythropoietin differs markedly from that disclosed by Amgen's specification. Of particular significance, TKT (1) utilizes the endogenous rather than exogenous EPO gene; and (2) places its promoter upstream from rather than adjacent to the EPO gene. *See* Trial Ex. 1 at 24:1922, 24:28-32, 25:55-61; Trial Tr. at 165:19-21, 174:18 to 175:4, 372:14-19, 375:19-25, 376:20 to 381:1, 537:18-20, 1330:2-5. Thus, relying on the same reasoning that gave rise to the non-infringement ruling with respect to the '698 patent, the Court here finds that TKT does not infringe literally or under the document of equivalents Claim 7 of the '349 patent. Nevertheless, judgment of

infringement will enter with respect to Claims 1, 3, 4, and 6 of the '349 patent.

2. *The '933 Patent*

Claim 1 of the '933 patent is directed to non-naturally occurring EPO glycoprotein products having both the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and glycosylation which differs from that of human urinary EPO. Trial Ex. 2 at 38:17-21. Each claim limitation and the evidence relating thereto is considered seriatim.

First, the Court finds that HMR4396 is "non-naturally occurring," which the Court interpreted as meaning "not occurring in nature" or "would not occur but for human intervention," *see supra* Section II.H, at 36-39. One technique contemplated by this claim limitation is recombinant DNA technology which in simple terms, consists of linking two DNAs that are not normally together. Trial Tr. at 129:5-6. A construct consisting of two recombined DNA sequences is not naturally occurring in the sense that but for human intervention, they would not exist together in a DNA strand. *Id.* at 128:4 to 129:3. Moreover, any glycoproteins obtained from transcription of recombinant DNA and translation of the resulting mRNA as well as the pharmaceutical composition derived therefrom, are non-naturally occurring.

The evidence is clear that HMR4396 is only made by manipulation of R223 cells which would not otherwise naturally produce EPO. In fact, TKT's witness, Dr. Kingston testified directly that "the EPO region in [TKT's) R223 cells is non-naturally occurring, yes." *Id.* at 1417:20-21; *see also* Treco Designated Dep. at 505:20 to 506:4 (recognizing that R223 cells are not found in nature). Dr. Kingston also agreed that the HT1080 cells used to make the R223 cells do not naturally produce EPO. Trial Tr. at 1503:8-12. In addition, Dr. Tlsty specifically described the dramatic changes she

discovered upon comparing R223 cells with their parent HT1080 cells through karyotypic and FISH testing. *Id.* at 844:21 to 847:7, 858:21 to 859:4, 882:12-20. Her tests revealed that the EPO DNA located on chromosome 7 of the HT1080 cells had been replicated, significantly rearranged, and scattered throughout various segments of chromosomal material within R223 cells. *See* Trial Exs. 90, 151-54. The inference suggested by her testimony and accepted by the Court is that the condition of the R223 cells could not have happened without human intervention—most importantly TKT's amplifying the EPO DNA within the R223 cells. Thus, the Court finds that HMR4396 is non-naturally occurring as that claim is employed in the '933 patent.

Second, the Court finds that HMR4396 is an erythropoietin glycoprotein product, as is required by the claim. A protein is a linear molecule usually consisting of more than fifty amino acids linked together in a specific sequence. Proteins form the key structural elements in cells and participate in nearly all cellular activities. As the name suggests, a glycoprotein is a protein that has undergone glycosylation,[34] a process whereby groups (or chains) of carbohydrate (or sugar) residues chemically attach to the protein as the protein is synthesized.[35] Thus, in order for HMR4396 to constitute an erythropoietin glycoprotein product, it must contain the EPO protein and that protein must have chemically attached carbohydrate chains. Such is the case here. In fact, TKT admitted during the *Markman* hearing that its product "is an erythropoietin polypeptide that has glycosylation . . . ." Tr. of *Markman* Hr'g, Vol. II at 134:14-15. Furthermore, in light of

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[34] The process of glycosylation is discussed in more detail below. *See infra* Section IV.E.2, at 129-32.

[35] As explained by one expert in the field of glycobiology, "the word glyco is really of Greek origin . . . from the word glykys, meaning sweet, and it's been used for many, many years to denote anything having to do with carbohydrates and carbohydrate structure." Trial Tr. at 569:17-20.

the substantial amount of trial time devoted to the specific glycosylation characteristics of HMR4396, there can be no doubt that HMR4396 is an erythropoietin glycoprotein product.

Third, HMR4396 meets the claim limitation that the glycoprotein product have "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." Trial Ex. 2 at 38:18-20. In the Amended Answer, TKT explained that in preliminary animal testing, its product had "the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." Am. Answer ¶ 26. Then, during the *Markman* hearing, in response to the Court's question whether HMR4396 "causes bone marrow cells to increase production of reticulocytes and red blood cells in vivo," counsel for TKT admitted, "The answer to that is yes." Tr. of *Markman* Hr'g, Vol. II at 134:1720. In light of these admissions, the Court finds that HMR4396 literally infringes the claim limitation requiring the EPO glycoprotein to have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells.

The fourth and final claim limitation is the stickiest. Claim 1 of the '933 patent claims an EPO glycoprotein "having glycosylation which differs from that of human urinary erythropoietin." Trial Ex. 2 at 38:20-21. The Court has construed the phrase "glycosylation which differs" to mean "glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." Tr. of *Markman* Hr'g, Vol. III at 102:15-23. Thus, in order for Amgen to prove literal infringement on this point, the claim language requires evidence that persuasively establishes detectable differ-

ences between the glycosylation of TKT's product and the glycosylation of human urinary EPO.

Amgen put forth Dr. Richard D. Cummings, a professor of biochemistry and molecular biology at the University of Oklahoma Health Center in Oklahoma City, to testify regarding glycosylation. Trial Tr. at 560:21 to 561:1. Dr. Cummings explained that glycosylation is directed by the complement of enzymes that cells contain as well as the structure of the protein itself. *Id.* at 576:4-9. Proteins are often depicted in a linear fashion by their amino acid sequence, *see, e.g.*, Trial Ex. 1 Fig.6, but in reality, proteins are naturally folded, Trial Tr. at 576:9-10. As a result, the folded protein may be more or less accessible to the various enzymes that affect glycosylation. *Id.* at 576:10-15. Just as the expression of proteins is regulated genetically by DNA, the expression of the enzymes that place carbohydrates on proteins is also genetically regulated. *Id.* at 576:18-21. Thus, DNA directs certain cells not only to express certain proteins, but also to express specific enzymes that act upon those proteins. In particular, the enzymes known as glycosyltransferases transfer sugars from a donor onto the protein. *Id.* at 577:17-22. This process is what is referred to as "glycosylation."

In 1983, there were a number of analytical techniques available for detecting differences in glycosylation between different glycoproteins. *Id.* at 578:13-17. One such technique was known as SDS-PAGE. *Id.* at 578:20-24, 581:16. In order to perform SDS-PAGE experiments, the protein of interest is incubated with a detergent called sodium dedecyl sulfate, which binds to the protein, denatures it so that it is more or less linearized, and contributes a strong negative charge to the protein. *Id.* at 581:14-20. The protein is then placed in an SDS-PAGE apparatus that contains an electric field. *Id.* at 581:19. Then, because opposites attract, the protein will migrate to the positive electric charge. *Id.* at 581:21-22. The protein's migration is impeded by an acrylamide gel that is

applied to the apparatus. *Id.* at 581:22-24. One can determine the size of the protein based upon the speed at which it travels through the gel. Thus, "[t]hings that are small move faster and things that are big move slower." *Id.* at 581:24 to 582:1. Because the apparatus contains a number of lanes or wells, different substances can be placed side-by-side for comparison. When compared with known standards, a substance's molecular weight can be approximated. *Id.* at 583:8-15. Substances with low molecular weights move quickly while those with high molecular weights migrate slowly through the gel. One can also identify the relative size of the protein's glycosylation by using SDS-PAGE. *Id.* at 592:14-20. The experimenter can compare a glycosylated protein with the same type of protein that has been treated so as to cause deglycosylation. *See id.* at 582:811. As one might expect, a deglycosylated protein migrates farther on SDS-PAGE than the glycosylated protein because the latter is weighed down by its attached sugar chains. The difference between the distances that these proteins migrate through the acrylamide gel represents the apparent molecular weight of the glycosylation of that protein. *Id.* at 590:16-22, 592:14-20.

The experimenter can analyze the data provided by the SDS-PAGE test by employing the Western blot. First, the researcher takes the SDS-PAGE gel and attaches it onto a piece of paper called nitrocellulose. *Id.* at 582:19-20. After the nitrocellulose and acrylamide come together, an electric field is run horizontally through the gel, which transfers the proteins from the gel to the paper. *Id.* at 582:20-24. The paper has both molecular weight markers stained with color that act as standards and different proteins. *Id.* at 582:25 to 583:1. The nitrocellulose can then be stained with an antibody to identify a desired protein. *Id.* at 583:2-3. Once identified, the relevant protein's migration can be compared with the migration of the known standards, yielding a molecular weight approximation. *See id.* at 583:4-6, 19-23; 590:24 to 591:9. More precisely, one can observe differences in the

distances each substance migrates on the nitrocellulose. This technique is known as Western blotting.

Another technique employed by those skilled in the art in 1983 was isolectric focusing ("IEF"). IEF resembles SDS-PAGE except that sodium dedecyl sulfate is not introduced to the protein to provide a negative charge to the sample. *See id.* at 588:5-23. Instead, in an IEF experiment, the protein's inherent charge moves the protein top to bottom through the gel which contains a pH gradient. *Id.* at 588:8-13, 589:13-16. Varying types of sugars have varying charges, so for example, all other things being equal, proteins that have a large number of sialic acids are more negatively charged than proteins that have fewer sialic acids. *See id.* at 605:9-16. The protein migrates until its inherent charges are neutralized by the pH gradient. *Id.* at 588:13-15, 605:13-16. "So in general if you had a collection . . . of erythropoietin glycoproteins differing in sialylation, one could distinguish the different glycoforms by IEF gel . . . ." *Id.* at 605:24 to 606:2. Similarly, by employing IEF, a researcher can separate and identify proteins on the basis of their charge. *Id.* at 588:18-23.

Dr. Cummings also explained that the patent disclosed Amgen's use of these techniques in order to show glycosylation differences between its recombinant EPO glycoproteins and the naturally occurring prior art urinary EPO glycoproteins. *See id.* at 614:9-25; Trial Ex. 1 at 28:33-50. As disclosed in Column 28 of the patent, these studies revealed that according to Western blot and SDS-PAGE analyses, "the CHO-produced EPO material had a somewhat higher molecular weight than the COS-1 expression product which, in turn, was slightly larger than the pooled source human urinary extract." Trial Ex. 1 at 28:38-41. Amgen scientists then treated the proteins with neuraminidase, which removes the sialic acids from the protein. *Id.* at 28:42-43; Trial Tr. at 611:17-18. Following neuraminidase treatment, the COS-1 and CHO recombinant products had approximately equal

apparent molecular weights, but were both nonetheless larger than the resulting asialo human urinary extract. *See* Trial Ex. 1 at 28:42-46; Trial Tr. at 613:1-11. Amgen then treated the CHO and human urinary products with endoglycosidase F, which removes not only sialic acids, but also any other carbohydrate chains attached to the protein. Trial Ex. 1 at 28:46-48. Amgen scientists discovered that the CHO and urinary products were "substantially homogenous products having essentially identical molecular weight characteristics." *Id.* at 28:49-50; Trial Tr. At 613:12-17. The conclusion to be drawn from this series of tests is that the difference in the apparent molecular weights of recombinant and urinary EPO products on SDS-PAGE and Western blot is explained by differences in glycosylation between the two types of EPO glycoproteins. Trial Tr. at 613:23 to 614:1. ("[T]he results then demonstrate the difference in mobility of these proteins compared to the urinary derived EPO is due to a difference in asparagine glycosylation and due to a difference in sialic acid content."). In light of this data reported in Column 28, one skilled in the art in 1983 would understand that "the recombinant proteins are glycosylated differently than the naturally-occurring protein, and that these differences can be revealed by running an SDS-PAGE and doing a western blot as described here." *Id.* at 620:1-5.

In the final paragraph of Column 28, Amgen disclosed the results of another set of experiments intended to show differences in glycosylation between recombinant and urinary EPO products. Trial Ex. 1 at 28:51-67. Amgen performed "carbohydrate analyses" in order to identify the individual monosaccharide sugar residues present on both the EPO derived from CHO cells and derived from urine. *See id.*; Trial Tr. at 620:20-23.

> [I]n this experiment the glycoprotein is taken and hydrolyzed in the presence of acid . . . and that cleaves the bonds between the amino acids, cleaves the bonds

> between the individual sugar residues. . . . [A]ll the sugars then are present unlinked to each other as individual monosaccharides. They can be labeled and separated by some chromatographic method. So that, say the sialic acids are separated from the N-acetylglucosamines and Fucose and so forth.

Trial Tr. at 621:15-24. Once all of the sugars are separated and identified, their relative distribution can be calculated. *Id.* at 621:24 to 622:1. In particular, one type of sugar is designated as one, and the other sugars are compared by their abundance in relation to the standardized sugar. *Id.* at 622:1-5. In the nomenclature of the patent specification, one can identify the carbohydrate constitution values expressed as molar ratios of the carbohydrates in the product. Trial Ex. 1 at 28:56-58. Using this method, the patent reveals that the recombinant EPO product contains a higher ratio of N-acetylneuraminic acid (.998) than the urinary EPO product (.930).[36] *Id.* at 28:56-66. This difference in the carbohydrate constitution values between the recombinant and urinary EPO glycoproteins is "consistent with the Western blot and SDS-PAGE analysis described above." *Id.* at 28:66-67.

Dr. Cummings also conducted experiments in order to determine whether there are glycosylation differences between TKT's product and urinary EPO. Trial Tr. at 629:18-

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[36] The patent also reports an erroneous Hexose value for the CHO derived EPO product (15.09) compared to the urinary derived EPO product (1.73). Trial Ex. 1 at 28:56-66. Dr. Cummings explained that "it would be obvious to anybody else in the field who looks at these values" that the recombinant product's Hexose value was erroneous because neither he nor anybody else that he knew had ever seen such high Hexose content in a glycoprotein. Trial Tr. at 623:5-9, 17-19. Apparently, because sugars are prevalent—our clothes are made of glucose which is a Hexose—contamination of the carbohydrate analysis can occur. *Id.* at 623:11-16. Dr. Cummings suspected that such contamination explained the high Hexose values reported in the patent specification. *Id.* at 623:16-19.

23. He concluded that "the recombinant erythropoietin made by TKT is clearly different in glycosylation from the naturally occurring erythropoietin in human urine." *Id.* at 629:18-20. Specifically, Dr. Cummings performed both SDS-PAGE and Western blot analyses and IEF experiments to compare the products. *See id.* at 629:25 to 630:9, 648:19-21.

His SDS-PAGE and Western blot analyses indicate that HMR4396 has a higher apparent molecular weight than the naturally occurring EPO and that the difference is due to differences in glycosylation. *Id.* at 630:5-9. Following the techniques described in the Amgen patent specification, Dr. Cummings ran the SDS-PAGE gels both prior to and after deglycosylation treatment with sialidase and endoglycosidase. *See id.* at 631:8-15. After deglycosylation, the mobility of the compared proteins was substantially similar, raising the inference that differences in migration on the initial gel were due to differences in glycosylation. *Id.* at 631:13-21. Dr. Cummings repeated the experiments and obtained similar results leading to the same conclusion: TKT's EPO product has glycosylation which differs from that of human urinary EPO. *See id.* at 645:17 to 648:20.

In conducting IEF experiments, Dr. Cummings compared HMR4396 with urinary EPO. *Id.* at 649:11-14. The urinary EPO traveled farther down the gel than the recombinant EPO indicating that the urinary EPO is more acidic than HMR4396's EPO. *Id.* at 649:15-17. Dr. Cummings concluded that these results were consistent with the SDS-PAGE results indicating that TKT's recombinant EPO is glycosylated differently (probably due to the sialic acids) than urinary EPO. *Id.* at 649:17-21.

If left undisturbed by effective cross-examination or credible contradictory evidence, Dr. Cummings' testimony regarding his experiments would discharge Amgen's duty of showing by a preponderance of the evidence that HMR4396 has glycosylation which differs from that of human urinary

EPO. In such a scenario, a finding of literal infringement as to this claim limitation in the '933 patent would follow. TKT, however, made great headway on these matters and, in the end, cast so much doubt upon Amgen's proof that a finding of no literal infringement is warranted.

Though ultimately deemed unpersuasive, TKT first argued that the SDS-PAGE experiments its expert conducted, which compared GA-EPO with urinary EPO samples, revealed no difference in glycosylation because there was no detectable difference between the migration of GA-EPO and two of the urinary EPO samples. *See* Trial Exs. 138, 139, 2012, 2451, 2452; Trial Tr. at 2319:10 to 2321:5, 2340:20-23; Strickland Designated Dep. (Sept. 14, 1999) at 288-356. In particular, TKT compared GA-EPO samples with urinary EPO samples prepared by Dr. Tom Strickland following the Miyake procedure referenced in the patent. *See* Trial Exs. 138, 139, 2012; Strickland Designated Dep. (Sept. 14, 1999) at 288 356. TKT compared GA-EPO to two urinary EPO samples (uEPO2 and uEPO3) purified from the 17 mM DEAE-agarose fraction and a urinary EPO sample (uEPO1) purified from the 30 mM DEAE-agarose fraction. Trial Tr. at 2316:10 to 2319:9, 2343:5-15. TKT contends that because there was no detectable difference between the migration of GA-EPO and the uEPO2 and uEPO3 urinary EPO samples, their glycosylation must be identical.

TKT's contention fails as a matter of logic. The fact that Dr. Strickland's experiments reveal that the GA-EPO and two urinary EPO samples migrated an equal distance does not imply that their *glycosylation* is the same. Rather, one can infer only from this that the apparent molecular weights of these glycoproteins is the same. *See id.* at 581:21-24. In order to make the additional inference that the two proteins have the same glycosylation, one must first treat the glycoproteins with enzymes that cause deglycosylation, and then these deglycosylated products must be run through the SDS-PAGE

gel and compared. *See id.* at 582:8-11, 592:14-20. If the *deglycosylated* products travel down the gel the same distance (implying an equivalent apparent molecular weight), only then one can infer that the fact that the GA-EPO and two urinary EPO samples migrated an equal distance was not due to a difference in glycosylation. TKT failed to do this latter step, making Strickland's experiment inconclusive as to whether the glycosylation of the GA-EPO and urinary EPO differs. Thus, the Court finds TKT's SDS-PAGE experiments involving GA-EPO and uEPO unpersuasive in rebutting Amgen's prima facie showing through Dr. Cummings of glycosylation differences between GA-EPO and urinary EPO.

TKT's second tack, however, leads it through the breakers and into a safe harbor. In short, TKT's evidence shows that different urinary EPO samples can themselves have glycosylation differences depending on how they are purified. As a result, Dr. Cummings' evidence that GA-EPO differs from one type of urinary EPO is insufficient as matter of fact to prove literal infringement.

Returning to the claim language, as construed by the Court, "human urinary erythropoietin" contains no limitation as to the source, purity, or method of preparation of the EPO other than that it be "derived from human urine." Tr. of *Markman* Hr'g, Vol. III at 112; Trial Tr. at 702:9 to 703:18, 1843:1-11; *supra* Section II.J, at 42-44. The claim language also provides no guidance regarding levels of EPO yield in or biological activity of the urinary EPO preparation. Trial Tr. at 703:19 to 704:7. Moreover, although the patent specification refers to different urinary EPO preparations and methods for purifying urinary EPO, including the methods of Miyake et al. and Yanagawa et al., Trial Ex. 1 at 7:3-23, 8:9-15; Trial Tr. at 633:5-21, 1978:12 to 1979:6, 2731:12-14, in the portion of the patent specification describing glycosylation experiments with recombinant and urinary EPO products, no specific information is provided regarding how to select a urinary

EPO preparation for purposes of comparison, *see* Trial Ex. 1 at 28:33-50. Furthermore, the patent does not specify which urinary EPO preparation ought be used as a standard in determining whether a particular EPO sample has glycosylation which differs from that of human urinary EPO. Trial Tr. at 786:6 to 787:11, 1846:23-25, 1978:12 to 1980:1, 1981:20 to 1982:1. Though a skilled worker might be able to guess, such an artisan reading the '933 patent would not know which urinary erythropoietin preparation should be used as a standard in making the comparison described in the patent and called for by the claims. *See id.* at 1981:20 to 1982:7.

This lack of direction regarding the selection of a urinary EPO standard is important because different urinary EPO preparations have different glycosylation due to the action of "glycosyltransferases," which are enzymes that add carbohydrate structures to the EPO molecule, *see id.* at 575:12 to 577:15, 1847:13 to 1848:5. The EPO molecule contains four carbohydrate chains attached at specific amino acids on the protein. Denoted by asterisks in Figure 6 of the patent, three of these four chains are "N-linked" chains and are linked to the amino acid arginine at positions 24, 38, and 83 of the EPO-molecule, while the fourth chain is an "O-linked" chain and is linked to the amino acid serine at position 126. *Id.* at 1962:22 to 1963:6. As explained in greater detail during trial, the heterogeneity of EPO glycosylation is manifested by differences in the number, type, and arrangement of the individual monosaccharides that make up the carbohydrate chains. *See id.* at 606:4-20, 759:19 to 767:18, 1847:13 to 1849:22, 1964:3 to 1966:10. For example, all other things being equal, an EPO preparation consisting of EPO molecules that have a higher number of tetra-antennary structures would migrate differently on SDS-PAGE from an EPO preparation consisting of EPO molecules that have a higher number of triantennary carbohydrate structures. *Id.* at 763:14 to 764:1.

In addition, the use of different methods of purifying erythropoietin results in different glycosylated erythropoietin

populations. TKT submitted evidence indicating, for instance, that after undergoing ion exchange column chromatography, one sample of EPO separates into different glycosylated populations. *Id.* at 1966:14 to 1968:2, 2136:9-16, 2161:25 to 2162:13; Strickland Designated Dep. (Feb. 8, 2000) at 71:5 to 72:10. In fact, another of Amgen's patents describes the separation of EPO molecules that differ from each other by as few as one sialic acid using ion exchange column chromatography. *See* Trial Ex. 2130 at 14:57 to 15:4. In 1984, there were several other purification methods available to ordinary skilled workers. *See* Trial Exs. 42, 2012, 2233, 2235-36, 2247, 2252, 2333, 2440; Trial Tr. at 632:13 to 634:1, 1846:19-22, 1970:6 to 1979:8, 2189:16 to 2190:25, 2193:9 to 2194:15, 2197:2-19. The 1977 Miyake et al. publication, for example, describes the purification from the same starting material of two homogeneous urinary EPO preparations (Fraction II and Fraction IIIA) that had about the same potency in terms of biological activity. *See* Trial Ex. 2012 at 5558, 5562-63. Fractions II and IIIA, later known as α and β urinary EPO, Trial Ex. 2439 at 2294; Trial Tr. at 772:25 to 773:5, 1972:2-6, had different carbohydrate compositions and, therefore, differed from each other in glycosylation, *see* Trial Ex. 2023 at A45537; Trial Ex. 2439 at A25197; Trial Tr. 1972:816. Thus, these two uEPO preparations, though produced by the same procedure (Miyake) and derived from the same batch of material, nonetheless had different glycosylation.

Additional experiments conducted by Amgen scientists in 1984 showed that different urinary EPO preparations had different glycosylation. In the spring of 1984, in conjunction with scientists from Kirin, Dr. Strickland purified EPO from the urine of a single patient using a modified Miyake procedure. *See* Trial Ex. 2013 at A 90211-48; Trial Ex. 2400 at A 95587; Strickland Dep. (Sept. 13, 1999) at 86:13 to 88:23, 91:5-10. This urinary EPO was referred to as "Lot 82" urinary EPO. Strickland Designated Dep. (Sept. 13, 1999) at

88:2-12, 91:5-10. Dr. Joan Egrie conducted a series of SDS-PAGE experiments comparing Lot 82 EPO with a uEPO received from Dr. Eugene Goldwasser.[37] Dr. Egrie compared the preparations side-by-side on the same gel and concluded that the Lot 82 and Goldwasser uEPO samples migrated differently on SDS-PAGE, with the Lot 82 material having a higher molecular weight. *See* Trial Ex. 126 at A4719-23, A4724-25, A4743-49, A4758-65, A4788-93; Trial Ex. 2400 at A95587-98; Trial Ex. 2094 at A4913-21; Trial Tr. at 2287:6 to 2291:15. After performing additional tests before and after treatment with enzymes effecting deglycosylation, she also concluded that this difference in migration was due to differences in glycosylation. In particular, the Lot 82 and Goldwasser uEPO migrated differently before enzymatic treatment, and the two preparations migrated the same after such treatment. These tests confirmed that the difference in apparent molecular weight between Lot 82 and Goldwasser uEPO was caused by differences in glycosylation. *See* Trial Ex. 126 at A4558-65; Trial Ex. 2400 at A95587, A9559091, A95593-98; Trial Tr. at 2290:1 to 2293:9. Dr. Egrie came to the same conclusion when she compared a commercially available urinary EPO from Alpha-Therapeutics to Goldwasser uEPO. *See* Trial Ex. 126 at A4788-93; Trial Ex. 2400 at A95590-91. Moreover, Dr. Egrie's various SDS-PAGE experiments reveal that different uEPOs have varying glycosylation. Trial Tr. at 2289:13 to 2294:9, 2294:22 to 2295:5. In light of this evidence, a skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification methods could have different glycosylation. *id.* at 1846:12-25, 1966:14 to 1967:1, 1970:10-25, 2303:9-17; *see also* Browne Designated Dep. (Sept. 17, 1999)

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[37] Though Dr. Cummings criticized Dr. Egrie's methodology in these experiments, the Court finds that the use of iodinated samples did not affect the results she obtained. Trial Tr. 807:25 to 808:9, 2293:10 to 2295:25.

at 226:3 to 227:19. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target.

The claim language of the '933 patent, however, presupposes that the glycosylation of urinary erythropoietin is a fixed, identifiable marker against which the glycosylation of recombinant EPOS can be measured. Yet, how can one prove that a recombinant EPO has glycosylation which differs from that of urinary EPO when the glycosylation of urinary EPO itself varies? The Court need not answer this conundrum. All that need be said is that Amgen's showing that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs is insufficient to carry its burden of proving by a preponderance of the evidence that TKT infringes this claim limitation. Consequently, the Court finds that HMR4396 does not literally infringe Claim 1 of the '933 patent.

Claim 2 is dependent upon Claim 1 and differs only in that the glycoprotein product's molecular weight, as measured by SDS-PAGE, must be higher than that of human urinary EPO. Trial Ex. 2 at 38:22-25. Because of its dependency upon non-infringed Claim 1, the Court finds no literal infringement of Claim 2. In addition, the Court finds that Amgen's evidence that the GA-EPO has a higher molecular weight than urinary EPO suffers from the same deficiency as its proof regarding their differences in glycosylation because the molecular weights of uEPOs vary as well.[38] A finding of literal non-

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[38] Amgen's Dr. Strickland attempted to purify human urinary EPO using the Miyake method. *See* Trial Exs. 138, 139; Trial Tr. at 2310:20 to 2311:4; Strickland Designated Dep. (Sept. 14, 1999) at 288-356. Dr. Strickland discovered that the EPO separated into two different fractions—a 17 mM fraction and a 30 mM fraction—from which he collected uEPO. *See* Trial Ex. 139 at AM 77 000101, AM 77 000138-42, AM 77 000152-53; Trial Ex. 2461; Trial Tr. at 2311:7 to 2312:1, 2343:5-15. Dr. Strickland separately purified EPO from each fraction and subjected the

infringement of Claim 2 of the '933 patent therefore follows.

Claim 9 recites a "pharmaceutical composition comprising an effective amount [of] a glycoprotein product effective for erythropoietin therapy according to Claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier." Trial Ex. 2 at 39:1-4. Because, in this litigation, Claim 9 is dependent upon either Claim 1 or Claim 2 and the Court has found that GA-EPO literally infringes neither, so too with respect to Claim 9.[39] Thus, because Amgen's proof on the limitation requiring the erythropoietin glycoprotein to have glycosylation which differs from that of human urinary erythropoietin was insufficient, the Court finds that all three

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EPO obtained therefrom to SDS-PAGE. *See* Trial Ex. 139 at AM 77 000138-42, AM 77 000152-53; Trial Ex. 2012 at 5563; Trial Ex. 2316 at AM 77 000271-72; Trial Tr. at 2317:15 to 2318:19. These SDS-PAGE experiments revealed that the EPO obtained from the 17 mM fraction migrated more slowly than that of the 30 mM fraction, thus indicating the 17mM fraction's higher apparent molecular weight. *See* Trial Ex. 139 at AM 77 000152-53; Trial Ex. 2316 at AM 77 000271-76; Trial Tr. at 2312:2 to 2314:2; Strickland Designated Dep. (Feb. 8, 2000) at 57:24 to 63:6; Strickland Designated Dep. (Sept. 14, 1999) at 352:6 to 353:8. TKT also compared the 17 mM and 30 mM urinary EPO fractions on SDS-PAGE and found that two 17 mM fractions (identified as uEPO2 and uEPO3) migrated more slowly than the 30 mM purified sample (uEPO1). *See* Trial Ex. 2447 at HMR806130; 2449-52; Trial Tr. at 2343:5 to 2344:21, 2351:14 to 2352:10.

[39] But for its dependency upon non-infringed claims, judgment of infringement on Claim 9 would be appropriate in light of the evidence regarding the other limitations in Claim 9. HMR4396 Injection is a pharmaceutical composition. *See* Trial Ex. 18 at IND000019; Trial Ex. 27 at IND501303-04; Hancock Designated Dep. at 242:9 to 243:25, 282:8-21. It also contains an amount of a glycoprotein product effective for erythropoietin therapy. *See* Tr. of *Markman* Hr'g, Vol. II at 135:25 to 136:2. Finally, HMR4396 Injection contains a phosphate buffer, which is a pharmaceutically acceptable diluent. *See* Tr. of Summ. J. Hr'g (Apr. 26, 2000) at 65; Hancock Designated Dep. at 242:22 to 243:11.

of the asserted claims of the '933 patent are not literally infringed.

Amgen's evidence is also insufficient to show infringement under the doctrine of equivalents. Amgen points to evidence submitted during trial that tends to show that HMR4396 is nothing more than a "me too" product. Trial Tr. 2231:9-10 (defining "me too" product as "one that simply copies an existing product"). Documentary and testimonial evidence indicates that the goal of the HMR4396 project was to make a product therapeutically equivalent, rather than superior, to Amgen's EPOGEN®. *See* Trial Ex. 160 at HMR 007088; Trial Ex. 162 at HMR 017347; Trial Ex. 16S at HMR 028663; Trial Ex. 166 at TKT 005008; Trial Ex. 170 at HMR 346024-26; Trial Ex. 173; Trial Ex. 180 at HMR 305229; Trial Ex. 196 at HMR 042121; Trial Tr. at 2224:10-22, 2229:18 to 2230:11, 2230:22 to 2233:22, 2236:19 to 2240:2; Hancock Designated Dep. at 206:22 to 209:23; Fike Designated Dep. at 65:15-20. Moreover, it appears that TKT achieved nothing more than equivalence: TKT admitted to the FDA that its clinical trials show that HMR4396 and EPOGEN® are equivalent in their clinical properties, and that patients given HMR4396 had more negative reactions than those given EPOGEN®. *See* Trial Ex. 122 at HMR 801225, 801229, 801231, 801233, 801281-83; Trial Ex. 123 at HMR 801510; Trial Tr. at 492:8 to 493:1, 556:25 to 557:9, 1949:2 to 1953:2; Hahner Designated Dep. at 348:14 to 350:7, 351:20 to 352:20, 410:8 to 411:15, 444:16 to 447:18; Hancock Designated Dep. at 251:25 to 253:10. Thus, the Court finds that HMR4396 has no demonstrable advantages over EPOGEN®. *See* Trial Ex. 159 at HMR 005237; Trial Ex. 177 at HMR 413257; Trial Tr. at 2229:15 to 2230:11; Hahner Designated Dep. at 265:2-6; Treco Designated Dep. at 663:23 to 664:17.

However, this general finding is insufficient to establish infringement under the doctrine of equivalents. A claim limi-

tation is equivalently present in an accused product if there are only "insubstantial differences" between the limitation and the corresponding aspects of the product. *CAE Screenplates Inc.* v. *Heinrich Fiedler GMBH & Co.*, 224 F.3d 1308, 1319 (Fed. Cir. 2000). "The usual test of the substantiality of the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element." *Upjohn Co.* v. *Mova Pharm. Co.*, 225 F.3d 1306, 1309 (Fed. Cir. 2000); *see also Graver Tank Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950). The Supreme Court has recently explained in *Warner-Jenkinson Co.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), that the doctrine of equivalents is limited, however, so that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole." *Id.* at 29. Thus, in order to show infringement under the doctrine of equivalents, one must prove not only that the accused product is *generally* equivalent to the patented product, but also that a *specific element* of the accused product is substantially equivalent to that *same element* of the patented product.

The Court finds that Amgen's evidence regarding general therapeutic similarities between HMR4396 and EPOGEN® fails to meet the Supreme Court's requirement that plaintiffs asserting the doctrine of equivalents must produce evidence with respect "to individual elements of the claim, not to the invention as a whole." *Warner-Jenkinson,* 520 U.S. at 29. None of this evidence persuades the Court of the precise—and more salient—point that the claim term requiring glycosylation which differs from that of human urinary erythropoietin is met equivalently by HMR4396. Accordingly, it is insufficient to ground Amgen's claim under the doctrine of equivalents.

Amgen did, however, present some evidence that moved closer to the specificity required by the Supreme Court. In particular, Amgen presented evidence that any glycosylation pattern differences between HMR4396 and EPOGEN® are relatively insubstantial. *See* Trial Ex. 168 at HMR 102737; Trial Ex. 171 at HMR 314992; Trial Ex. 173 at TKT 006145; Trial Ex. 182 at L002293; Trial Ex. 183 at L001918; Trial Ex. 197 at HMR 472507; Trial Tr. at 2245:22 to 2252:23. Amgen's theory is thus: if the glycosylation of EPOGEN® differs from that of human urinary erythropoietin and glycosylation differences between HMR4396 and EPOGEN® are relatively insubstantial, then the glycosylation of HMR4396 must similarly differ from that of human urinary erythropoietin. The theory itself is quite tenuous, and the proof of it unpersuasive. Because Amgen failed both to establish the necessary facts by a preponderance of the evidence and to tie these inferences together in a persuasive manner, the Court finds that it failed to shoulder its burden of proof. Despite Amgen's rapid bailing, the doctrine of equivalents does not rescue its sinking infringement ship. Consequently, the Court determines that the '933 patent is not infringed.

3. *The '080 Patent*

The asserted independent claims of the '080 patent pertain to erythropoietin glycoproteins that (1) have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells; (2) comprise the mature erythropoietin amino acid sequence of Figure 6; and (3) are either non-naturally occurring (Claim 2) or isolated but not from human urine (Claim 3). Trial Ex. 3 at 38:32-50. Dependent Claim 4 lays claim to a pharmaceutical composition comprising a therapeutically effective amount of the glycoprotein product according to Claims 2 or 3. *Id.* at 38:51-53. As previously explained, the Court found at the close of Amgen's infringement case that the '080 patent was not literally infringed. *See supra* Section IV.C.1, at 61-66.

Though defeated in the engagement over literal infringement, Amgen has not retreated from the infringement battlefield. Instead, it sails on under the doctrine of equivalents. In analyzing whether each and every limitation of the claim is literally or equivalently present, *CAE Screenplates Inc.*, 224 F.3d at 1318-19, the Court first addresses those claim terms that are literally present in HMR4396.

The Court has previously held or it is undisputed that HMR4396 (1) is an "erythropoietin glycoprotein," Joint Pretrial Mem. at 5, ¶ 27; Tr. of *Markman* Hr'g, Vol. II at 134:12-16, 136:13-14; (2) has "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells," Joint Pretrial Mem. at 5, ¶ 24; Tr. of *Markman* Hr'g, Vol. II at 134:17-20, 136:15-16; *see also supra* Section IV.E.2, 127-28; (3) is not isolated from human urine, Trial Ex. 19 at 506, 547 (IND for HMR4396); *see also* Am. Answer ¶ 25 (admitting that GA-EPO is not isolated from human urine); (4) is a "non-naturally occurring" erythropoietin glycoprotein, *see supra* Section IV.E.2, at 125-27; and (5) with respect to the additional limitations contained in dependent Claim 4, HMR4396 Injection is a "pharmaceutical composition" comprising a "therapeutically effective amount [of] an erythropoietin glycoprotein product," Joint Pretrial Mem. at 5, ¶ 26; Tr. of *Markman* Hr'g, Vol. II at 130:17-20, 136:13-14; *see also supra* Sections III.A, III.B.

Claim 2 of the '080 patent claims an "isolated" erythropoietin glycoprotein having certain additional characteristics. Trial Ex. 3 at 38:39. Although the Court did not construe the term "isolated" during the *Markman* hearing, the term's meaning can be inferred from its use in the specification. For example, the patent refers to "[i]nitial attempts to isolate erythropoietin from urine," Trial Ex. 1 at 7:3, and it later states that "[o]ther isolation techniques utilized to obtain purified erythropoietin involve immunological procedures."

Id. at 7:43-44; *see also id.* at 11:15-19. After considering these excerpts from the patent, Dr. Lodish testified that one of ordinary skill in the art would understand the term "isolate" to mean "to recover in pure form." Trial Tr. at 193:4 to 194:3. The Court agrees. The Court also agrees with Dr. Lodish that HMR4396 is isolated as that term is used in the patent. *Id.* at 211:22 to 212:2. The IND for HMR4396 identifies a combination of column chromatography and ultrafiltration steps to recover erythropoietin in pure form from its cultured cells. *See* Trial Ex. 19 at IND000506. Thus, Amgen has proven by a preponderance of the evidence that HMR4396 literally meets the requirement of Claim 2 that the erythropoietin glycoprotein be "isolated."

Thus, the Court finds as matter of fact that all the limitations in the asserted claims of the '080 patent are literally infringed by HMR4396 or HMR4396 Injection except for the limitation that the erythropoietin glycoprotein comprise "the mature erythropoietin amino acid sequence of FIG. 6," Trial Ex. 3 at 38:36, 38:43, 38:48-49. The Court found previously that because TKT's cells produce an erythropoietin glycoprotein comprising a 165 amino acid sequence rather than the 166 amino acid sequence depicted in Figure 6, HMR4396 did not literally infringe the asserted claims of the '080 patent. *See supra* Section IV.C.1, at 61-66. Amgen contends, however, that this claim limitation is infringed under the doctrine of equivalents. As a result, the question boils down to whether, despite having a 165 amino acid sequence, HMR4396 performs substantially the same function in substantially the same way to obtain substantially the same result as an erythropoietin glycoprotein containing 166 amino acids. The Court finds that it does and, consequently, concludes that HMR4396 infringes the '080 patent under the doctrine of equivalents.

The question focuses narrowly on the effect of the arginine at the 166 position of Figure 6. The 165 amino acid EPO

sequence of HMR4396 is identical to amino acids 1 through 165 in Figure 6. *See* Trial Ex. 18 at IND000019; Trial Ex. 23 at IND002191; Trial Ex. 25 at IND002357; Trial Ex. 29 at IND002470, 002480; Trial Ex. 2299 at L7828; Trial Tr. at 175:19-25, 199:15 to 211:13, 213:210. Likewise, the glycosylation sites of HMR4396 are identical to those depicted in Figure 6. *See* Trial Ex. 25 at IND002357; Trial Tr. at 202:17-20. As a result, the only difference between the amino acid sequence of HMR4396 and that of Figure 6 is the additional amino acid, arginine, at position 166, or at the "C-terminus," of Figure 6.

The Court finds that Amgen has shown by a preponderance of the evidence that the presence or lack of this arginine at the C-terminus of these glycoproteins does not make them materially different. An erythropoietin glycoprotein containing either amino acid sequence has the same conformational structure and biological activity. Importantly, the Court finds that the lack of the arginine residue at the C-terminus does not affect the *in vivo* biological activity of the EPO product. To prove this point, Amgen presented evidence regarding a study comparing erythropoietin lacking four amino acids normally found at the C-terminus (163-166) and the normal protein, referred to in the study as "wild-type." *See* Trial Ex. 54 at IND000181. Employing biological assays, the researchers discovered that such changes at the C-terminus neither affect the biological activity of the protein nor inhibit proper secretion from the cells. *See id.*; Trial Tr. 214:6-22, 215:21 to 216:20. The clear inference from this evidence is that if the glycoprotein is substantially the same when its last four amino acids are removed, then the absence of but one of these four should not cause any significant differences. Trial Tr. at 214:20-22. The Court accepts this inference and is persuaded by it.

In reaching his conclusion that the arginine does not materially affect the erythropoietin glycoprotein, Dr. Lodish

relied upon an article that identified the portions of the erythropoietin protein that are important for binding to the EPO receptor. *See id.* at 218:9 to 219:10. According to Dr. Lodish, the paper concludes that the C-terminus does not form part of the binding site. *Id.* at 219:1-3. As a result, one of ordinary skill in the art "would expect small changes at the C terminus would have no effect on the binding property." *Id.* at 219:4-5. Similarly, Dr. Lodish relied upon experiments performed at Amgen that, according to him, showed that an erythropoietin glycoprotein containing an arginine residue at position 166 functions in the same way to achieve the same result as an erythropoietin glycoprotein lacking the arginine. *See id.* at 219:11 to 220:2, 223:10-11. The Court credits Dr. Lodish's testimony on these matters.

TKT attempted to whittle away at Amgen's evidence on equivalence. On cross-examination, Dr. Lodish admitted that a change in the amino acid sequence of a protein can in many cases have adverse immunological effects in the clinical use of that protein. *See id.* at 501:12-21. TKT also elicited testimony from Dr. Kingston explaining that a change in even just one amino acid can have a significant effect on the clinical function of a protein. *Id.* at 1245:22 to 1246:3. While these general statements may be true, they are ineffective in rebutting Amgen's more precise evidence specifically tailored to slight variations in the amino acid sequence of erythropoietin. Similarly, TKT's evidence comparing GA-EPO to Amgen's EPOGEN® is either irrelevant or too speculative to warrant the Court to find that GA-EPO is significantly different from EPOGEN®, and more importantly, that any such difference is due to GA-EPO's absence of the arginine at position 166. *See* Trial Ex. 122 at HMR 801231; Trial Tr. at 2225:15 to 2227:17.

Thus, the Court finds that Amgen has proven by a preponderance of the evidence that, despite lacking the arginine at position 166, HMR4396 performs substantially the same

function in substantially the same way to obtain substantially the same result as an erythropoietin glycoprotein containing 166 amino acids. Consequently, Amgen has proved that HMR4396 meets each of the limitations of the asserted claims of the '080 patent either literally or by equivalence.

In order to reach this conclusion, the Court necessarily rejects TKT's contention that prosecution history estoppel precludes Amgen's reliance on the doctrine of equivalents. TKT argues that during the prosecution of the '080 patent, Amgen added the limitation "the mature erythropoietin amino acid sequence of FIG. 6" to distinguish its glycoprotein claims from those of the already issued '933 patent, which were not limited by a precise amino acid sequence. In particular, following an interview with Examiner Martinell in December of 1996, *see* Trial Ex. 3 Tab 4, Amgen amended the pending claims to limit the glycoprotein claimed to one having the mature erythropoietin amino acid sequence of Figure 6, *see* Trial Ex. 3 Tab 6 at 162. In submitting these amendments, Amgen specifically told the Patent Office that the added limitation distinguished its pending '080 claims from those of the '933 patent: "Applicant notes that claims 69, 70 and 71[, corresponding to issued Claims 1, 2, and 3 of the '080 patent,] all differ in scope from glycoprotein claim 1 of U.S. 5,547,933 in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6." *Id.* at 164.

The Court finds, however, that estoppel is inappropriate in this circumstance because Amgen did not add this claim limitation in an attempt to overcome a rejection, to avoid prior art, *see Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 3031 (1997), or indeed for any reason related to the statutory requirements for a patent. *See Festo Corp.* v. *Shoketso Kinzoku Kogyo Kabushiki Co., Ltd.*, No. 95-1066, 2000 WL 1753646, at *6 (Fed. Cir. Nov. 29, 2000) (noting that prosecution history estoppel is not limited to

avoiding prior art but includes any reason that relates to the statutory requirements of a patent). The limits of the doctrine of prosecution history estoppel were recently explained by the Supreme Court. In *Warner-Jenkinson*, the petitioner, not unlike TKT here, sought to extend the theory such that "any surrender of subject matter during patent prosecution, regardless of the reason for such surrender, precludes recapturing any part of that subject matter, even if it is equivalent to the matter expressly claimed." 520 U.S. at 30. The Supreme Court responded:

> But petitioner reaches too far in arguing that the reason for an amendment during patent prosecution is irrelevant to any subsequent estoppel. In each of our cases cited by petitioner and by the dissent below, prosecution history estoppel was tied to amendments made to avoid the prior art, or otherwise to address a specific concern—such as obviousness—that arguably would have rendered the claimed subject matter unpatentable.

Id. at 30-31. After quickly reviewing a handful of its estoppel cases, the Supreme Court continued:

> It is telling that in each case this Court probed the reasoning behind the Patent Office's insistence upon a change in the claims. In each instance, a change was demanded because the claim as otherwise written was viewed as not describing a patentable invention at all—typically because what it described was encompassed within the prior art. . . . Our prior cases have consistently applied prosecution history estoppel only where claims have been amended for a limited set of reasons, and we see no substantial cause for requiring a more rigid rule invoking an estoppel regardless of the reasons for a change.

Id. at 31-32. Thus, Amgen's evidence under the doctrine of equivalents is not defeated by the mere fact that Amgen's

amendment added the limitation that the claimed glycoprotein have the mature erythropoietin amino acid sequence of Figure 6.

The Court must instead endeavor to identify the reason such limitation was added. This search for purpose is made more difficult where, as here, there is nothing in the file wrapper as of the date of the amendment indicating that the claims were objectionable to the Patent Office. Such a notice followed by amendment would, of course, raise the inference that the subsequent amendment was intended to address the Patent Office's precise concern. Absent such clear history, however, the search for the purpose of the amendment becomes more thorny. Nonetheless, according to *Warner-Jenkinson*, Amgen bears the burden of showing that the amendment was not submitted "to avoid the prior art, or otherwise to address a specific concern—such as obviousness—that arguably would have rendered the claimed subject matter unpatentable." *Id.* at 30-31.

Reviewing the file wrapper, it appears that the amendment was submitted for the not uncommon purpose of distinguishing the language of the '080 claims from that of the glycoprotein claims of the '933 patent. By stating that the claims of the '080 patent "differ in scope from claim 1 of U.S. Patent 5,547,933 in specifying that the [claims of the '080 patent contain] the mature erythropoietin sequence of Figure 6," Trial Ex. 3 Tab 6 at 164, Amgen was simply directing the Patent Office to claim language that demonstrated that "same invention" type double patenting did not apply. By this amendment, Amgen was not attempting to distinguish the claims of the '080 patent from prior art because, due to the fact that both the '080 and the '933 patents arise from a common disclosure, the '933 patent is not prior to the '080 patent. Instead, Amgen was merely exercising its long-accepted right to press alternative claims covering different aspects of its invention.

Nor does Amgen's terminal disclaimer give rise to estoppel. Amgen filed a terminal disclaimer, causing the term of the '080 patent to end on the same day as the term of the '933 patent, for the purpose of mooting any possible non-statutory, obviousness-type double patenting rejection. *See id.* One might expect that such an attempt to avoid an objection relating to double patenting would be grounds for estoppel. Yet terminal disclaimers do not operate to effect estoppel: the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection. *Quad Envtl. Techs. Corp.* v. *Union Sanitary Dist.*, 946 F.2d 870, 874 (Fed. Cir. 1991); *see also Wooster Brush Co.* v. *Newell Operating Co.*, No. 99-1393, 2000 WL 748074, at *5 (Fed. Cir. June 9, 2000) (unpublished opinion); *Sash Controls, Inc.* v. *Talon, L.L.C.*, Nos. 98-1152, 98-1182, 1999 WL 110546, at *3 (Fed. Cir. Jan. 27, 1999) (unpublished opinion).[40] There is no indication in the Federal Circuit's recent *Festo* decision that this limitation to estoppel is no longer good law. Without additional evidence, the Court will not infer from the terminal disclaimer that Amgen sought to overcome a meritorious prior art rejection.

At its core, what estoppel seeks to prevent is reliance upon the doctrine of equivalents when the prosecution history makes clear that the patentee abandoned the precise aspect of a competitor's product that infringes by equivalency. Only in this circumstance is it fair to limit the effective scope of the claimed invention. Simply put, the evidence does not show

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[40] For the propriety of citing an unpublished opinion, see *Anastasoff* v. *United States*, 223 F.3d 898, 899-905 (8th Cir.) (R. Arnold, J.) (holding that unpublished opinions have precedential effect), *vacated as moot*, No. 99-3917, 2000 WL 1863092 (8th Cir. Dec. 18, 2000), *Giese* v. *Pierce Chemical Co.*, 43 F. Supp. 2d 98, 103 (D. Mass. 1999) (relying on unpublished opinions' persuasive authority), and Richard S. Arnold, *Unpublished Opinions: A Comment*, 1 J. App. Prac. & Process 219 (1999).

that the patentee abandoned glycoproteins having a mature erythropoietin amino acid sequence of 165 residues for the purpose of avoiding prior art, obviousness, or any other patentability reasons. Thus, Amgen has met its burden under *Warner-Jenkinson.* As a result, the Court will not estop Amgen from contending that HMR4396 infringes the Figure 6 limitation by equivalency. Therefore, in light of its earlier findings that HMR4396 meets each limitation either literally or by an equivalent, the Court concludes that HMR4396 infringes the asserted claims of the '080 patent.

F. *The Remaining Defenses*[41]

It is appropriate again to pause for a moment to emphasize the importance of the particular procedural approach that this Court used in conducting the *Markman* hearing. Because this Court conducted its claim construction independent of rather than in the context of the infringement issues raised in the summary judgment hearing, it avoided any risk of conflating the legal issue of claim construction with the factual issue of infringement. This case provides an ideal example of the magnitude of the consequences of such conflation.

Had this Court constructed Amgen's claim language in the context of the issues of infringement, the risk of "neatly" disposing of the case by narrowly construing Amgen's claims would have loomed very large. Indeed, had the Court narrowly construed Amgen's claims, this already overlong opinion would have long been at an end because infringement would most likely have been decided on the summary judgment record, leaving TKT free and clear as a non-infringer and Amgen (though losing this case) would have retained its patent monopoly against all other comers.

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[41] It will be recalled that the Court rejected TK's anticipation and obviousness defenses at the close of its case pursuant to Federal Rule of Civil Procedure 52(c), setting out its findings and rulings in Section IV.D., at 75-110. TK's remaining defenses are addressed in this section.

However, by conducting its claim construction independent of the issues of infringement, this Court was not even tempted by such a narrow construction; rather, the Court properly performed its judicial function of legal construction by giving credence to the plain and ordinary meaning to one skilled in the art of Amgen's claims despite the breadth of such a construction.

It is only by walking the line strictly between legal construction and fact finding that this Court has stumbled upon the complex factual questions that are presented in this opinion. Now that the Court has found TKT to be an infringer under the Court's broad claim construction of Amgen's claims, that very construction provides TKT with a strong riposte—to destroy Amgen's patents entirely, even though this means opening the field to not only TKT, but also the world. The stakes in this phase of the battle are thus infinitely higher. Thus far, Amgen has largely secured the broad patent protection it has claimed.[42] A failure in this phase of the case could prove fatal, however, as it would extinguish Amgen's patent protection altogether.

As the contending parties sail into the culminating melee, however, Amgen is aided by two strong, though not impregnable, legal principles. First, as the owner of issued patents, Amgen is entitled to the "presumption of validity." The presumption of validity is, in patent law, not a true evidentiary presumption at all, i.e. an aid to proof that vanishes once the opponent produces evidence to rebut the presumed fact. Fed. R. Evid. 301; William G. Young et al., *Massachusetts Evidentiary Standards* 44 (2000); *see also*

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[42] Because it can be claimed that Amgen's broad patent monopoly serves as a "blocking" patent to prevent advances in research and development by others, some commentators claim that, in lieu of licensing, a doctrine of patent "fair use" ought be developed. *See, e.g.*, Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 Colum. L. Rev. 1177, 1192-93 (2000).

Paul J. Liacos et al., *Handbook of Massachusetts Evidence* § 5.5.3, at 230 (7th ed. 1999). Rather, the presumption of validity shifts the burden of proof to TKT and places on it not only the burden of going forward but also the burden of persuasion itself. *See Canon Computer Sys., Inc.* v. *Nu-Kote Int'l, Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998). Moreover, in order to overcome the presumption of validity, TKT must convince the Court, not by a fair preponderance but by clear and convincing evidence, to adopt one or more of its defenses. *Sibia Neurosciences, Inc.* v. *Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). As will be seen in this most complex case, at least in part, it is this heightened standard of proof to which Amgen ultimately clings as a piece of flotsam among the wreckage of its evidentiary presentation.

1. Inequitable Conduct

TKT rigorously contends that Amgen's patents ought be declared unenforceable because they were obtained as a result of inequitable conduct. In order to obtain a patent, an applicant must first persuade the Patent Office, and more precisely its Examiner, that the applicant invented a patentable invention. During the course of this period of negotiation between the applicant and the Patent Office, the applicant provides significant information to the Patent Office in an attempt to prove that the patent should issue. As one might expect, for the Patent Office to determine intelligently whether a patent should issue, an applicant must disclose all information known to be material to patentability. Thus, when the applicant ultimately obtains the patent, but does so by either withholding material information from, or by misrepresenting material facts to, the Patent Office while possessing the intent to deceive the Patent Office, the patents are rendered unenforceable. *Baxter Int'l, Inc.* v. *McGaw, Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998).

To prove the defense of inequitable conduct, a defendant must show that the patentee withheld material information from the patent examiner or submitted false material information, with the intent to deceive or mislead the examiner into allowing the patent. *Upjohn Co.* v. *Moval Pharm. Corp.*, 225 F.3d 1306, 1312 (Fed. Cir. 2000) (citing *Kingsdown Med. Consultants, Ltd.* v. *Hollister Inc.*, 863 F.2d 867, 872 [Fed. Cir. 1988]). Both materiality and intent to deceive are independent elements, each of which must be proven by clear and convincing evidence. *See Kingsdown*, 863 F.2d at 872; *see also Manville Sales Corp.* v. *Paramount Sys., Inc.*, 917 F.2d 544, 552 (Fed. Cir. 1990). Information is material "'where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent.'" *Upjohn*, 225 F.3d at 1312 (quoting 37 C.F.R. § 1.56 [1988] [amended 1992, 2000]); *see also Molins PLC* v. *Textron, Inc.*, 48 F.3d 1172, 1179 (Fed. Cir. 1995).[43] A reference, however, need not be disclosed to the examiner if it is merely cumulative of, or less material than, other references already before the examiner.

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[43] This formulation of the rule regarding materiality was in force from 1977 to 1992. In 1992 and again in 2000, the Patent and Trademark Office amended Rule 56. The rule, as amended in 1992, provided that:

> [I]nformation is material to patentability when it is not cumulative to information already of record or being made of record in the application, and (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or (2) It refutes, or is inconsistent with, a position the applicant takes in: (i) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b) (1992) (amended 2000). The Federal Circuit, however, has made clear that this amendment is not retroactive. *See Molins*, 48 F.3d at 1179 n.8. As a result, because the prosecution of the patents-in-suit spanned the period from 1983 to 1999, and thereby straddled the amendment of Rule 56, the previous rule governs the conduct of Amgen's agents between 1983 and 1992 and the subsequent rule governs the conduct of Amgen's agents between 1992 and 1999.

Upjohn, 225 F.3d at 1312; *Baxter Int'l*, 149 F.3d at 1328. In assessing intent, the Court should consider any "evidence indicative of good faith." *Kingsdown*, 862 F.2d at 876. Finally, and importantly, the intent to deceive cannot be inferred "solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." *Hebert* v. *Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). Each of TKT's various contentions will be addressed in turn.[44]

a. The Goldwasser Clinical Study

TKT contends that Amgen's representatives withheld from the Patent Office Dr. Goldwasser's urinary erythropoietin clinical study. TKT argues that the study was relevant to the patentability of Claim 1 of the '422 patent. In particular, TKT alleges that the study reveals that Dr. Goldwasser's urinary erythropoietin preparation contained a therapeutically effective amount of in vivo biologically active erythropoietin. As such, it constituted prior art that would have anticipated or rendered obvious Amgen's pharmaceutical composition claim had it been appropriately disclosed by Amgen's representatives. Consequently, contends TKT, Claim 1 of the '422 patent ought not be enforced.

The Court is not persuaded. Importantly, it appears to this Court that, although Amgen could have drawn more attention to the Goldwasser study, Amgen actually did disclose it. Specifically, during interference proceedings involving applications leading to the patents-in-suit, Amgen disclosed Dr. Goldwasser's sworn testimony before the United States

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[44] The Court recognizes that Amgen objects to TKT's pursuit of a number of separate allegations of inequitable conduct because, it argues, many of these allegations were not pled in the amended answer or otherwise timely disclosed to Amgen such that it could effectively prepare a defense. In light of the substantive outcome of these matters, however, resolution of this procedural dispute is unnecessary.

International Trade Commission ("ITC") to the Board of Patent Appeals and Interferences. In that testimony, Dr. Goldwasser described the unavailability of therapeutically effective amounts of EPO despite his abortive trial with human urinary erythropoietin. *See* Trial Ex. 209 at AM 17 027722-23. Furthermore, the ITC Administrative Law Judge, Sidney Harris, referred to this testimony in his Initial Determination Opinion. *See* Trial Ex. 101 at AM 17 027597. Amgen submitted Judge Harris' opinion to the Patent Office during prosecution and the Examiner, who was specifically provided with a copy, reviewed the opinion and cited its findings of fact as evidence demonstrating the non-obviousness of Dr. Lin's claimed compositions. *See* Trial Ex. 102 at AM 17 027580-81; Trial Ex. 109 at AM 27 015059; Trial Ex. 2198 at 214-15.

TKT replies, however, that Amgen may not rely upon its disclosure to the Interference Branch to satisfy its duty of disclosure during ex parte prosecution with an Examiner. *See Mech. Plastic Corp.* v. *Rawlplug Co.*, 14 U.S.P.Q.2d (BNA) 1058, 1061 (S.D.N.Y. 1989); *A.B. Dick Co.* v. *Burroughs Corp.*, 617 F. Supp. 1382, 1395 (N.D. Ill. 1985), *aff'd*, 798 F.2d 1392 (Fed. Cir. 1986); *Gen. Elec. Co.* v. *United States*, 206 U.S.P.Q. (BNA) 260, 280 (Ct. Cl. Trial Div. 1979). In *A.B. Dick*, for instance, an applicant failed to disclose material prior art during initial ex parte proceedings, cited the art during an interference, and then again failed to cite the art during post-interference ex parte prosecution. *A.B. Dick*, 617 F. Supp. at 1392-93. Interestingly, the examiner nonetheless learned of the art without the applicant's assistance. *Id.* at 1392. Notwithstanding the disclosure during the interference and that the examiner actually learned of the art on his own, the district court held that the subsequently issued

patent was unenforceable because of the applicant's failure to call the prior art to the examiner's attention:

> [I]nitial disclosure of prior art in the interference proceeding (as one of a large number of references in one of a large number of exhibits) does not satisfy the applicant's duty of candor—particularly where the prior art had been undisclosed for some years before that and later remained undisclosed by the applicant at the time he was urging issuance of the patent . . . .

Id. at 1397. The Federal Circuit affirmed, noting that "The PTO cannot realistically be thought of as the equivalent (say) of a small law firm office, in which notice to one person may fairly be deemed notice to all. It is not necessarily true that the PTO Examining Division will have access to proofs filed in the course of an interference." *A.B. Dick Co.* v. *Burroughs Corp.*, 798 F.2d 1392, 1399 n.7 (Fed. Cir. 1986) (quoting *A.B. Dick*, 617 F. Supp. at 1397).

This case is distinguishable, however, because here the prosecution history demonstrates that the Examiner reviewed and considered the Interference decision and record. After resolution of the Interference proceedings, Examiner David L. Fitzgerald recorded on the file wrapper of the application that led to both the '933 and '080 patents, that he had received and, for a two-month period, reviewed the Interference record and decision. The Examiner's notes state:

> Reviewed parent file 675,298
> Reviewed Interference file #102,334
> Reviewed published Intf. Decision (*Fritsch v. Lin*) & *Amgen v. Chugai* (18 U.S.P.Q.2d @1016)
> Oct-Nov 1993
> Fitzgerald DL

Trial Ex. 2 Tab 58 at 715. Subsequent notations indicate that the Examining Division understood the import of the Interference proceedings. *Id.* Tab 34 at 405; *see also id.* Tab 23 at 284-87. TKT responds by arguing that the Court should not

be persuaded that disclosure to Examiner Fitzgerald is sufficient since Examiner Martinell, rather than Examiner Fitzgerald, was the primary examiner involved in issuing the patents-in-suit. The *Manual of Patent Examining Procedure*, however, directs that a previous examiner's searches and actions must be given full faith and credit by all subsequent examiners. *Manual of Patent Examining Procedure* §§ 704, 706.04 (7th ed. 1998). Thus, unlike TKT's cited cases, the evidence here is clear that the Examining Division reviewed and considered the Interference record and the Board's decision. As a result, in this case as in others, disclosure to the Interference branch satisfied Amgen's duty of candor to the Patent Office. *See E.I. Du Pont de Nemours & Co.* v. *Phillips Petroleum Co.*, 656 F. Supp. 1343, 1376 (D. Del. 1987), *rev'd on other grounds*, 849 F.2d 1430, 1439 (Fed. Cir. 1988).[45]

Admittedly, Amgen neither submitted the actual scientific data relating to the study to the Patent Office nor extensively described the Goldwasser study in any of its submissions. Nonetheless, in this circumstance, its disclosures narrowly discharge its duty of candor. Beyond this, it is more than clear to this Court that Amgen's representatives, by their disclosures, were not deliberately hiding the study from the Examiner. Reference to the study was made, and if the Examiner believed that further inquiry was required, the Examiner could have pursued it—it was the Examiner's choice not to.

Moreover, the Goldwasser study is cumulative in the sense that Amgen had, in any case, clearly disclosed to the Patent Office that human urinary erythropoietin was biologically active in vivo. The patent itself discusses at length the

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[45] The Court also notes that the Board is the ultimate arbiter of matters of patentability within the Patent Office and the examiner is bound by the Board's decision. *In re Van Geuns*, 946 F.2d 845, 847-48 (Fed. Cir. 1991); *Dewez* v. *Schleimer*, 2 U.S.P.Q.2d (BNA) 1636, 1637 (Bd. Pat. App. & Interf. 1987); *see also* 37 C.F.R. § 1.198 (2000).

biological activity of natural human erythropoietin, including human urinary erythropoietin. *See* Trial Ex. 1 at 5:48-53, 5:67 to 6:5, 7:10-17, 33:19-31; 35; Trial Tr. at 2994:3-19, 2995:15 to 2996:10. The original filed Claim 41 also reveals that Amgen believed not only that urinary EPO was biologically active, but also that it had the same biological activity of Dr. Lin's invention. Trial Ex. 2 Tab 1 at 110. Furthermore, the prosecution history makes clear that the Patent Office understood that "naturally occurring EPO" included human urinary EPO. *See id.* Tab 4 at 163 ("The disclosure of Miyake et al., shows isolation and purification of naturally derived EPO."). The Patent Office initially rejected original Claim 41 on the basis that it was anticipated by Miyake, which concerns the purification of human urinary EPO. *Id.* at 156, 163; *see also* Trial Ex. 35 at 5558; Trial Tr. at 2998:21 to 3001:5, 3004:15 to 3005:2. Amgen agreed that its recombinant EPO and human urinary EPO had the same in vivo biological activity, but distinguished its EPO by differences in glycosylation as well as differences in therapeutic effectiveness in treating patients with anemia. *See* Trial Ex. 2 Tab 6 at 175, 181-82; *id.* Tab 11 at 224, 227. Amgen also amended Claim 41 to highlight the specific in vivo biological activity characteristics shared by human urinary EPO and the recombinant EPO. *See id.* Tab 6 at 172. In light of this evidence, it seems clear that the Patent Office understood that recombinant and urinary EPO shared common in vivo biological effects. As a result, even if the Court agreed that Dr. Goldwasser's study showed a meaningful increase in reticulocyte and red blood cell production (a point which has not sufficiently been proven), it would have merely been cumulative.

Moreover, the Goldwasser study is not particularly material. At least two specific limitations of Claim 1 of the '422 patent essentially exclude Dr. Goldwasser's work. As the Court has previously explained, there is no evidence that Dr. Goldwasser's urinary EPO went beyond biological activity and accomplished therapeutic effectiveness, which is required

by Claim 1 of the '422 patent.[46] *See supra* Section IV.D.1.c, at 94-98. Likewise, Dr. Goldwasser's study did not involve an EPO purified from mammalian cells grown in culture, which is also required by Claim 1 of the '422 patent. Thus, in at least these two respects, Dr. Goldwasser's study was immaterial to the claim TKT seeks to defeat.

Most importantly, TKT has failed to produce any persuasive evidence that causes the Court to doubt the integrity of the individuals who bore the duty of shepherding the Amgen patent applications through the Patent and Trademark Office. Consequently, its charge of inequitable conduct utterly fails. Dr. Lin testified that he knew that Dr. Goldwasser had administered urinary EPO to two patients, but based upon the information that Dr. Goldwasser provided him, Dr. Lin concluded that urinary EPO was not therapeutically effective. *See* Trial Tr. at 947:21 to 948:12, 1097:1-14, 1098:8 to 1099:15, 1102:5 to 1103:2. In addition, those responsible for prosecuting the patents learned about the Goldwasser study from Dr. Goldwasser's testimony before the ITC, which highly criticized the value of the study. *See* Trial Ex. 209 at 22-24; Trial Tr. at 2925:9-21, 2961:19 to 2963:11. That the prosecuting attorneys understood that the Goldwasser study was a therapeutic failure negates an alleged intent to deceive. In fact, these attorneys actually disclosed the results of the study precisely because, in their minds, the failed test revealed a long felt need for therapeutically effective erythropoietin therapy. Thus, the Court finds that

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[46] In an attempt to escalate the materiality of the Goldwasser study vis-a-vis Claim 1 of the '422 patent, TKT conflates biological activity with therapeutic effect. In short, TKT contends that because the Goldwasser study presents data regarding the biological activity of human urinary EPO and since biological activity is equivalent to therapeutic effects, the Goldwasser study was highly relevant to the patentability of the claimed pharmaceutical composition. This conflation, however, is inappropriate, for these two phrases, though related, have entirely independent meanings. *See supra* Section IV.D.1.c, at 94-98.

Amgen provided the Goldwasser testimony and the ITC decision to the Patent Office because it believed that these sources revealed that a therapeutically effective erythropoietin product had not yet been obtained. Trial Tr. at 2963:1-11, 2969:16 to 2970:2. There was no intent to deceive. As a result, the Court concludes that TKT has failed to prove by clear and convincing evidence that Claim 1 of the '422 patent ought not be enforced because it was issued due to inequitable conduct on the part of Amgen's agents.

b. *Data Concerning Glycosylation Differences*

TKT also argues that the '933 patent should be rendered unenforceable because Amgen misrepresented some material data and withheld other experimental data relating to glycosylation differences between recombinant and human urinary erythropoietin. Claim 1 of the '933 patent covers erythropoietin glycoprotein products having glycosylation which differs from that of human urinary erythropoietin. TKT contends that Amgen's counsel knew that certain tests revealed that recombinant and human urinary EPOs were glycosylated to the same extent, but nonetheless failed to disclose these tests to the Patent Office. Instead, Amgen continued to stand by its representations in the patent and press claims asserting glycosylation differences. *See* Trial Ex. 1 at 28:33-50; Trial Ex. 2161 at 8-9; Trial Ex. 2164 at 4; Trial Tr. at 2862:5-18, 2879:12-25. If, indeed, these tests truly revealed that there were no detectable glycosylation differences between the two types of EPOs, then TKT will have satisfied its burden of proving materiality by clear and convincing evidence.

In November of 1984, Mr. Michael F. Borun, Amgen's patent counsel, received a package of information from Dr. Joan Egrie that was later placed in a folder labeled "Egrie Input." Trial Ex. 2400; Trial Tr. at 2836:9 to 2838:4, 2848:7-22. The Egrie Input included an SDS-PAGE gel that compared COS-1 produced recombinant EPO and Goldwasser's human urinary EPO standard. Trial Ex. 2400 at 20; Trial Tr.

at 2840:2 to 2841:10, 2842:9-16. Dr. Egrie reported that these EPOS "have the same molecular weight" and "that the recombinant EPO is glycosylated to the same extent as the native protein." Trial Ex. 2400 at 17, 22 ("Size of Gene's std. ~= size of COS cell-produced EPO as was seen in the prior sections . . . ."). The Egrie Input also included SDS-PAGE gels comparing CHO cell produced recombinant FPO and Lot 82 human urinary EPO; she explained that these gels indicated that the differing EPOs had the same molecular weight. *Id.* at 5a, 9, 22 ("CHO cell material . . . is ~ to Lot 82 EPO."). TKT contends that both of these tests were material to patentability and were intentionally shielded from the eyes of the Examiner even as Amgen's representatives were arguing to the Patent Office that glycosylation differences were apparent. TKT contends that this misrepresentation was compounded by Amgen's failure to correct the erroneous carbohydrate constitution values disclosed in the patent. Trial Ex. 1 at 28:51-57.

TKT also points to a number of Amgen publications that likewise reported that recombinant EPOs and human urinary EPOs migrated identically on SDS-PAGE gels and had the same molecular weight, suggesting that they were glycosylated the same. Trial Ex. 2406 at 243, 248-49 (Vapnek study); Trial Ex. 2398 at 218 (Egrie study); Trial Ex. 137 at 696-98 (Browne study). TKT also argues that some of Amgen's FDA submissions contradicted its arguments to the Patent Office. Trial Ex. 2023(b) at A 45481, A 45545 Fig. 50-20, A 45557 Fig. 50-26. The inference pressed by TKT is that Amgen, on the one hand, sought to put the FDA at ease by claiming that the glycosylation of CHO-produced recombinant EPO was just like that of naturally-occurring human urinary EPO, but on the other hand, attempted to persuade the Patent Office that recombinant EPO was truly novel over human urinary EPO by pointing to glycosylation differences.

Amgen responds to these charges. First, the Egrie Input was disclosed and considered by the Patent Office. In particular, Mr. Borun testified that it had been disclosed during the *Fritsch* v. *Lin* Interferences and used as an exhibit in the *Amgen* v. *Chugai* litigation. Trial Tr. at 2863:9 to 2864:4; *see also* Trial Ex. 105 (Egrie Input File, DX 316 in Civ. Action No. 87-2617-Y); Trial Ex. 206 at AM 17 057546-54, AM 17 05635-59 (Notice pursuant to 37 C.F.R. § 1.682[a] and Offer of Official Record Regarding Testimony of Egrie and Attachments submitted to the Patent Office in the Interferences). For example, Amgen submitted to the Board of Patent Appeals and Interferences a declaration of Dr. Egrie describing her various experiments, including the disputed SDS-PAGE experiments and the relevant laboratory notebook excerpts. Trial Ex. 2309 at AM 17 034807-09; *see also* Trial Exs. 104, 216, 217, 2118 (Lin Exs. 114-17 from *Fritsch* v. *Lin*, Interference Nos. 102,096, 102,097, and 102,334). Lin's Exhibit 115, for example, included pages sixty-five to seventy of Egrie Laboratory Notebook No. 633, Trial Ex. 104, and page sixty-nine of this notebook showed results from comparisons between CHO-produced EPO and various uEPO products. *Id.* at AM 17 079278. As already determined, Amgen's disclosure during the Interference proceedings discharges its duty of disclosure to the Examining Division as well.

Amgen also denies TKT's claim that it failed to disclose publications concluding that rEPO and uEPO glycosylation are the same. In an amendment filed on February 16, 1995, Amgen included a declaration by Dr. Cummings and attached a copy of the Browne publication, which TKT alleges was withheld from the Patent Office. Trial Ex. 210 at AM 27 020914, AM 27 020922, AM 27 021116. The Browne publication in turn cites an Egrie publication. *Id.* at AM 27 021119. The Browne publication explains that rEPO produced from both COS-1 and CHO cells "migrate identically" or are "indistinguishable." *Id.* at AM 27 021119, AM 27 021121. Amgen repeatedly cited this publication throughout

the prosecution of the patents-in-suit. Trial Ex. 3 Tab 7 at 182; Trial Ex. 4 Tab 10 at 181; Trial Ex. 5 Tab 10 at 209; Trial Ex. 6 Tab 27 at 266-501; Trial Ex. 6 Tab 36 at 559; Trial Ex. 137 Fig.4. Furthermore, in his declaration, Dr. Cummings discussed the Egrie publications and stated that the gels therein showed only that rEPO and uEPO were "similar but not identical" in their migration on SDS-PAGE. Trial Ex. 210 at AM 27 020644. The Court finds that in specifically identifying the Browne publication and discussing the Egrie publications, Amgen informed the Patent Office that these tests (and the conclusions derived therefrom) were circulating within the field.[47]

Additionally, Amgen made disclosures regarding rEPO and uEPO migrating identically during the Interference proceedings. Trial Ex. 97 (Interference Lin Ex. 218); Trial Ex. 111 (Interference Lin Ex. 396); Trial Ex. 112 at AM 17 028197-208 (Lin's Notice IV submitted in Interferences); Trial Ex. 113 at AM 17 024642-57 ("Publication 16," attached to Lin's Notice IV); Trial Ex. 218 (Notice IV by Lin submitted in Interferences). Moreover, although the ultimate issue for determination differed, the same allegations made here by TKT with respect to Dr. Egrie's work were resolved in favor of Amgen by the Patent Office during the Interference proceedings. *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1739, 1741-42 (Bd. Pat. App. & Interf. 1991); Trial Ex. 110 at 36 (8/12/91 Fritsch Reply Brief, Paper No. 169 in Interference No. 102,334); Trial Ex. 214 at AM 17 003716 (Fritsch Proposed Findings of Fact VI-17 at 227). Importantly, as explained above, the prosecution history reveals that the Examining Division of the Patent Office reviewed the

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[47] In any event, there is considerable doubt that the authors' conclusions were justified in light of the gels. *See, e.g.*, Trial Ex. 137 at 698; Trial Ex. 2399 at AM 49 028390; Trial Ex. 2398 at AM 47 012012-13; Trial Tr. at 684:4 to 686:15, 746:12 to 757:20, 1048:25 to 1057:24, 2379:10 to 2384:8.

Interference record and the Board's decision, as it is required to do.

As for the allegations regarding disclosures to the FDA, Amgen points out that the same gel that had earlier been submitted to the FDA (as well as the related conclusion that rEPO and uEPO migrate identically) was disclosed in the 1986 Egrie publication during the Interference. Trial Ex. 218 at AM 17 028197-208 (Lin Notice IV attaching Egrie et al., 172 *Immunobiology* 213-24 [1986]); *see also* Trial Ex. 207 at AM 17 049294-314 (Fritsch Ex. 399 from *Fritsch* v. *Lin*, Interference Nos. 102,096, 102,097, and 102,334). TKT's expert witness, Dr. Phillips W. Robbins also admitted that Amgen later told the FDA that there were differences in glycosylation between its rEPO and uEPO. Trial Tr. at 1999:10 to 2001:5. Thus, TKT's representation that Amgen was maintaining self-serving and conflicting messages to the FDA and the Patent Office is itself somewhat misleading.

At the same time, TKT has provided no evidence tending to show that the SDS-PAGE data set out in the patent was false or misleading. Mr. Borun received the data from Dr. Lin or members of Dr. Lin's staff and after Mr. Borun drafted the patent application, Dr. Lin reviewed and approved it. Trial Tr. at 1060:5-13, 2831:8-17, 2846:1-10, 2850:2-7; Borun Dep. at 26-27, 69-71. Mr. Borun, meanwhile, has no recollection of the Egrie Input document, which was produced from the files of his firm. Trial Tr. at 2836:37, 2848:7-22. In asserting the charge of inequitable conduct against Amgen, TKT is contending that Mr. Borun's lack of memory is deviously convenient. The Court is not persuaded that Mr. Borun has or had any such devious designs.

In any event, all of TKT's arguments surrounding the SDS-PAGE data are premised on one erroneous notion: that two EPOs that migrate identically on SDS-PAGE necessarily have the same glycosylation. Not so. As explained in the '933 infringement section of this decision, *supra* Section IV.E.2,

at 128-39, without additional SDS-PAGE tests comparing deglycosylated EPOS, one cannot make the more relevant determination as to glycosylation differences. Indeed, TKT's witness, Dr. Matsudaira, agreed that two EPO samples that migrate identically on SDS-PAGE do not necessarily have identical glycosylation. Trial Tr. 2372:22 to 2373:4. Moreover, the patent itself teaches that these subsequent tests should be performed. Trial Ex. 1 at 28:42-50. Importantly, portions of the Egrie Input ignored by TKT actually show an SDS-PAGE gel that compares CHO and COS-1 rEPOs with Goldwasser's uEPO both before and after at least partial deglycosylation. Trial Ex. 2093 at AM 87 015712; Trial Ex. 2400 at A95580; Trial Tr. at 2384-86. In reviewing this gel before partial deglycosylation, Dr. Egrie concluded that the "size of the CHO cell material is larger than COS or Gene's std." Trial Ex. 2400 at A95579 (22); Trial Tr. at 2384:2 to 2388:12; 2841:2-10. Then, after partial deglycosylation using neuraminidase treatment to remove the sialic acids, Dr. Egrie determined that "COS & CHO neuraminidase digestion products are both larger in size than digestion product obtained for Gene's crude EPO. This may suggest that there are differences in the remainder of the carbohydrate backbone of the recombinant material vs. Gene's std." Trial Ex. 2400 at A95579 (22); Trial Tr. at 2851:2-20. Thus, as both the patent and even the Egrie Input teach, one must perform SDS-PAGE tests not only before, but also after deglycosylation treatment to obtain information about the glycosylation of glycoproteins. Contrary to TKT's contentions, then, data in the Egrie Input is actually consistent (or at least not inconsistent) with Amgen's representations in the patent specification. Trial Ex. 126 at 69; Trial Ex. 2400 at A95591 (9), A95579 (22); Trial Tr. at 675:3 to 677:24, 2389:19 to 2390:1; *see also* Trial Ex. 2083 at 5005649-56 (69-72); Trial Tr. at 2385:3 to 2387:4, 2388:3 to 2390:1. Moreover, of particular significance here because the tests relied upon by TKT compare

only glycosylated EPOs, they are inconclusive and hence immaterial to the question of glycosylation differences.[48]

In addition, the erroneous nature of certain carbohydrate constitution values was disclosed through the Interference record to, and presumably considered by, the Patent Office. At the time the application was submitted, Dr. Lin and Mr. Borun believed the data to be accurate. Trial Tr. at 979:14 to 981:2, 2854:9-20, 2856:13 to 2857:2, 2859:10-17. During the Interference, the Board was informed that this carbohydrate data was incorrect. Trial Ex. 107 at AM 17 016877 (Brief for Senior Party Lin, Interference No. 102,334); Trial Ex. 110 at 42-43 (July 8, 1991 Brief for the Party Fritsch, Interference No. 102,334); Trial Tr. 1094:4-8; Borun Dep. (Nov. 23, 1999) at 146:17 to 147:8; *see also* Trial Ex. 214 at 223-25 (Fritsch Proposed Findings of Fact VI-6 to VI-12). Having the issue directly presented to it, the Board of Patent Appeals and Interferences determined that, despite the apparent error, "Lin's involved application, in addition to including the disputed hexose molar ratio data, also reports results of Western blot and SDS-PAGE analyses . . . coupled with results of endoglycosidase F enzyme treatment which . . . support the conclusion that there is indeed a difference in carbohydrate composition . . . ." *Lin*, 21 U.S.P.Q.2d (BNA) at 1741-42. The '933 prosecution history reveals that the Examining Division reviewed the Interference record and the Board's decision. Trial Ex. 2 at 284-87, 715. Amgen also informed the Patent Office that Genetics Institute, on appeal, had accused Amgen of inequitable conduct for failing to disclose the

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[48] Another test relied upon by TKT compares CHO material with Goldwasser and Lot 82 uEPO preparations. Trial Ex. 1 at A95578 (5a). Yet aided by the testimony of Drs. Cummings and Matsudaira, the Court finds that the CHO-expressed EPO did not migrate the same as the urinary EPOs. Trial Tr. at 676:2 to 677:24, 2388:3 to 2390:1; *see also* Trial Ex. 2 Tab 7, at 191 (Strickland Decl. [Nov. 30, 1988]); Strickland Dep. at 412-15.

erroneous nature of the carbohydrate data. Trial Ex. 205 at AM 17 011480-82 (Mar. 6, 1992 Petition under 37 C.F.R. § 1.182 at 10-12); Trial Tr. at 2986:24 to 2989:2. In addition, the Examiner also had before him the correct carbohydrate data for CHO-cell produced human EPO and uEPO provided in the Takeuchi and Sasaki references. Trial Ex. 2 at 448 (Aug. 16, 1994 Examiner's Action); Trial Ex. 210 at AM 27 020935-37, AM 27 021007-13, AM 27 021037-54 (Feb. 16, 1995 Amendment). Drs. Cummings and Robbins also agreed that the data was "grossly inaccurate" and that the error would have been readily identified by one of skill in the art in 1984. Trial Tr. at 622:19 to 624:6, 2130:20 to 2131:3. Furthermore, because the Patent Office had the correct carbohydrate constitution data as well as additional data confirming glycosylation differences, the incorrect data was immaterial to the patentability of the '933 claims. *Fritsch*, 21 U.S.P.Q.2d (BNA) at 1741-42; Trial Ex. 2 Tab 38 at 448; Trial Ex. 210 at AM 27 020935-37, AM 27 021007-13, AM 27 021037-54.

In light of the disclosures made directly to the Patent Office as well as those made indirectly through the Interference record, it is hard to believe that the Examiner was somehow left in the dark about the glycosylation differences dispute. Amgen presented significant data to the Examiner suggesting glycosylation differences and also disclosed apparently conflicting data. What more can Amgen fairly be expected to do? At some point, the applicant must be permitted the opportunity to argue that some data is more worthy of reliance than other data. Instead, TKT implies that Amgen should have stood by less reliable and incomplete data rather than data obtained from both glycosylated and deglycosylated EPOs. This expectation is unreasonable.

Thus, the Court finds that Amgen complied with its duty of candor with respect to data regarding glycosylation differences. Nonetheless, even if Amgen had withheld this data from the Patent Office, such withholding would not give rise

to a charge of inequitable conduct because TKT has failed to prove by clear and convincing evidence that this data was material or that it was withheld with the intent to deceive.

c. *The Human '293 Cell Experiments*

TKT also contends that the '422 and '349 patents should be rendered unenforceable because Amgen failed to disclose that its human host cell experiments performed with '293 cells were unsuccessful in producing high levels of EPO. Trial Tr. at 2974:12-17. In January of 1984, Amgen scientists measured EPO produced in both COS-1 and human cells referred to as '293 cells. The '293 cells produced about one hundred times less EPO than the COS-1 cells. Trial Ex. 2410 at AM 47 037787-88. While the COS cell data was added to the patent specification, the '293 cell data was not. Trial Tr. at 965:8 to 967:19. Amgen, however, continued to pursue claims like Claim 1 of the '422 patent which, Amgen argued, covered "any polypeptide having the amino acid sequence of EPO isolated from human urine and may be produced in human cells or in any other mammalian cells." Trial Ex. 2215 at AM 27 068753. TKT argues that Amgen withheld these '293 experiments because they would have cast significant doubt upon its assertion that its invention extended not only to CHO and COS cells but also to all mammalian cells including human cells.

As the Court will explain, contrary to TKT, the purpose of the '293 cell experiments was not to produce EPO in abundance, as TKT's argument implies. *See infra* Section IV.F.4.c, at 239-41. Instead, the purpose of the transient transfection experiments was to obtain a quick determination that Dr. Lin had, indeed, cloned the DNA sequence encoding human EPO. Trial Tr. at 428:10 to 429:12, 967:3-18, 1112:16 to 1113:11, 2111:19 to 2112:4, 2556:11 to 2556:3-8, 2559:1-6, 2568:8 to 2569:8, 2572:25 to 2573:4. Based upon Dr. Jeffrey Browne's contemporaneous notation of "Eureka," which he wrote in his laboratory notebook as he recorded the

results of the human cell experiments, it is clear to this Court that the experiments achieved their intended purpose. Trial Ex. 2350 at A 13932; *see also* Trial Tr. at 2111:19 to 2112:4, 2559:2-6, 2565:1 to 2567:25. If the goal of the experiments were high level expression, one of skill in the art would have known to employ the other techniques taught in the Amgen patent, such as the use of selectable markers, amplification, and sub-cloning. *See Johns Hopkins Univ.* v. *CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998); *Atlas Powder Co.* v. *E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Thus, these tests were not material to whether Amgen ought—as a matter of equitable conduct—be permitted to pursue cell and pharmaceutical claims that reach human cells. As will be seen, however, the question of enablement is a much closer one.

Moreover, Amgen disclosed the '293 experiments. Amgen repeatedly disclosed the decision in *Amgen, Inc.* v. *Chugai Pharm. Co.*, 13 U.S.P.Q.2d (BNA) 1737 (D. Mass. 1989) (Saris, M.J.), *aff'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1991). Trial Ex. 2 Tab 19 at 267; Trial Ex. 215 at AM 17 007065, AM 17 007068; Trial Tr. at 2925:22 to 2926:6. In her decision, Judge Saris explicitly refers to the '293 experiments and the fact that they successfully produced human EPO. She wrote, "By January 10, 1984, Amgen had expressed human EPO in human embryonic kidney cells called '293' cells . . . ." *Amgen*, 13 U.S.P.Q.2d (BNA) at 1748. Furthermore, during the Interference proceedings, Drs. Egrie and Browne submitted declarations to the Board in which they described these experiments and pointed the Board to the relevant laboratory notebooks. Trial Ex. 213 at AM 17 079613 (79) (Lin Ex. 112, Doc. Nos. L00982-85, L01001-05 [J. Egrie Laboratory Notebook No. 540 ("Transient Transfection in 293 hEPO—Are seeing expression!")]); Trial Ex. 217 at AM 17 009866 (Lin Ex. 116, Doc. Nos. L01101-04 [J. Lane Laboratory Notebook]); Trial Ex. 2116 (Lin Ex. 113, Doc. Nos. L01080-86 [J. Egrie's Laboratory

Notebook No. 569]); Trial Ex. 2032 (Mar. 18, 1991 Browne Decl. ¶¶ 7-15); Trial Ex. 2309 at AM 17 0034781-82, AM 17 034784-86 (Mar. 18, 1991 Egrie Decl. ¶¶ 5, 8-10). Recall that the Examiner reviewed the Interference record. Thus, the '293 experiments were actually disclosed to the Patent Office.

Even had Amgen withheld the '293 experiments from the Examiner and these allegedly unsuccessful experiments had been—as appears to be the case—material to patentability, the Court finds no evidence of an intent to deceive on the part of Amgen's representatives. Because these experiments achieved their purpose, Amgen's patent counsel, Mr. Stuart Watt, never believed that there was any reason to discuss these experiments with the examiner. Trial Tr. at 2974:12-17. The Court, therefore, concludes that if any material non-disclosure occurred, it did not occur for the intended purpose of deceiving the Patent Office into issuing patents covering human cells. Consequently, TKT's inequitable conduct defense fails with respect to the '293 cell experiments.

d. *The Present Litigation*

TKT also asserts that the '349 and '422 patents should not be enforced against it because Amgen withheld from the Patent Office not only that the patents-in-suit were the subject of litigation, but also that TKT's allegations in the lawsuit went right to the issue of patentability. The *Manual of Patent Examining Procedure* recommends disclosure of the existence of any lawsuit and any information from the lawsuit that is material to a patent application. *Manual of Patent Examining Procedure* § 2001.06 (7th ed. 1998). At the time the lawsuit was filed on April 15, 1997, only the '698, '080, and '933 patents had been issued. Trial Exs. 2-6. Amgen directly informed the Patent and Trademark Office of this lawsuit by letter the day after the complaint was filed. Trial Ex. 204 (Apr. 16, 1997 Peterson letter). In addition, Amgen filed a notice pursuant to 35 U.S.C. § 290 with the Clerk of the District Court of Massachusetts. Docket No. 6; *see also*

Haney v. *Timesavers,* 900 F. Supp. 1378 (D. Or. 1995). According to the statute, the Clerk is then required to give written notice to the Commissioner, "setting forth so far as known the names and addresses of the parties, name of the inventor, and the designating number of the patent upon which the action has been brought." 35 U.S.C. § 290. The Commissioner then is required to enter the receipt of such notices in the file of the relevant patent or patents. *Id.* What galls TKT here is that this notice only made reference to the '698, '080, and '933 patents, since they were the only patents-in-suit at the time. TKT argues that, because Amgen never told the Patent Office that the complaint was later amended to add charges of infringement of the '349 and '422 patents, Amgen acted unfairly. The Court is not convinced.

Initially, the Court notes that the Clerk actually bears some responsibility for disclosing additional patents-in-suit. The statute specifically states that "[i]f any other patent is subsequently included in the action [the Clerk] shall give like notice thereof." 35 U.S.C. § 290. Thus, although the duty of candor ultimately falls on the shoulders of the patent applicant, it seems reasonable for an applicant to expect that a court officer will perform statutory requirements.

Most importantly, TKT has not even begun to demonstrate that Amgen representatives possessed an intent to deceive the Patent Office in failing to provide specific notification regarding this litigation. With respect to its duty to disclose this litigation, Amgen's in-house counsel, Mr. Watt explained that he believed that Amgen satisfied its duty of disclosure by submitting the earlier notice. Trial Tr. at 2980:16, to 2983:22, 2985:24 to 2986:20, 3026:18 to 3027:10. Mr. Borun similarly testified. *Id.* at 2909:25 to 2910:14; 2913:8-25, 2915:7-21, 2921:5-16. The Court believes their testimony. Thus, even if the Court were to conclude that Amgen neglected its duty of candor in failing to update the Patent Office regarding this

litigation, TKT has failed to prove by clear and convincing evidence that Amgen did so with the intent to deceive.

In summary, TKT's proof of inequitable conduct with respect to each of these charges falls short of the mark. Although the directness of Amgen's disclosures varies depending on the particular piece of disputed information, one truth remains the same throughout: Amgen's representatives never intended to deceive the Patent Office. Consequently, a finding of inequitable conduct would be error and the Court does not so find on the complete trial record here.

2. *Written Description*

The first paragraph of 35 U.S.C. § 112 provides the basic requirements for the content of a patent specification:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . .

35 U.S.C. § 112 (1998). The sufficiency of the disclosure is measured as of the time of its filing. *Reiffin* v. *Microsoft Corp.*, 214 F.3d 1342, 1346 (Fed. Cir. 2000) (quoting *Application of Glass*, 492 F.2d 1228, 1232 [Ct. Cust. Pat. App. 1974])." The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Id.* at 1345. In order to serve this policy purpose, "the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Thus, section 112 requires this Court to determine whether Amgen's specification, considered as a whole, conveys to one of ordinary skill in the art either explicitly or inherently, that Dr. Lin invented the subject matter claimed in the patents-in-

suit. *Reiffin*, 214 F.3d at 1346; *see also Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

Of great significance here, however, once the Patent and Trademark Office issues the patent, the presumption of validity takes hold, *see* 35 U.S.C. § 282, requiring the Court to presume that the specification adequately describes the claimed subject matter. As a result, the burden falls upon TKT to prove by clear and convincing evidence that the specification fails to describe Amgen's claimed inventions. Although TKT persuades the Court by a preponderance of the evidence that the specification is deficient in some regards, it fails to make its case by clear and convincing evidence. Consequently, Amgen's patents narrowly survive TKT's written description challenge.

a. *'422 Patent*

As to the '422 patent, the Court initially disposes of those limitations that are clearly adequately described in the '422 patent. First, various passages of the specification explicitly address the characteristics of the claimed pharmaceutical composition. In the "Brief Summary" portion, the specification provides:

> Also comprehended by the invention are pharmaceutical compositions comprising effective amounts of polypeptide products of the invention together with suitable diluents, adjuvants and/or carriers which allow for provision of erythropoietin therapy, especially in the treatment of anemic disease states and most especially such anemic states as attend chronic renal failure.

Trial Ex. 1 at 12:1-7. Thus, one of ordinary skill in the art in 1984 would understand this paragraph to describe generally the pharmaceutical composition claimed in the '422 patent. *See* Trial Tr. at 1915:21 to 1916:23. In addition, other portions of the specification provide specific information regarding effective dosages and therapeutic effect in mice.

Trial Ex. 1 at 28:16-27, 33:50-61. Second, additional passages describe the purification of erythropoietin products from the host cell cytoplasm, membranes, or cell culture media. *See id.* at 11:8-14, 27:15-50, 28:29-32, 37:43-49. One of skill in the art in 1984 would have understood the Lin patent to describe techniques to obtain purified erythropoietin. Trial Tr. at 193:4 to 194:3. Third, the specification makes reference to various possible diluents, adjuvants, and carriers that could be used for delivery of erythropoietin therapy. Trial Ex. 1 at 33:61 to 34:27. One of ordinary skill in the art would have understood from these passages that Dr. Lin possessed the invention claimed in the '422 patent. The specification's detailed description of these elements quickly defeats TKT's contention that the written description is inadequate, save for one critical element that demands further analysis: mammalian cells.

Claim 1 of the '422 patent claims a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin which has been purified from *mammalian cells* grown in culture. Trial Ex. 6 at 38:39. TKT argues that the specification fails to describe EPO production from all mammalian cells.

The Court recognizes that Claim 1 of the '422 patent does not claim pharmaceutical compositions containing erythropoietin expressed from *all* mammalian cells, but only mammalian cells *grown in culture. Id.* at 38:39-40. Moreover, the Court finds that, based upon the knowledge possessed by one skilled in the art as well as the teachings in the specification, one of skill in the art in 1984 would have known to select one of the many mammalian cells that were available and suitable for continuous growth in culture in order to produce high levels of a desired protein. *See* Trial Tr. at 2671:21 to 2672:6; *see also id.* at 514:22-25.

Nonetheless, the Court agrees with TKT's central contention that the specification—at least explicitly—reports

production of EPO in host cells of only two mammalian species. Trial Ex. 1 at 23:4-15, 25:35-36, 25:39-42, 26:11-15. Examples 7 and 10 describe human erythropoietin production in monkey (COS-1) and hamster (CHO) cells, respectively. Trial Ex. 1 at 23:1 to 24:38, 25:29 to 29:7. Thus, the key question is squarely posed: do detailed descriptions of EPO production in these two mammalian species cell lines inform those skilled in the art that Dr. Lin possessed an invention encompassing EPO production in all mammalian cells grown in culture? After much reflection and despite some hesitancy, the Court concludes that they do.

The Court finds that the specification places all competitors on notice that its invention was not limited to erythropoietin products obtained only from COS-1 and CHO cells. For example, the specification announces that the invention contemplates the expression of polypeptides in eucaryotic hosts including "mammalian cells in culture" and refers to products of expression in "vertebrate (e.g., mammalian and a[v]ian) cells . . . ." *Id.* at 10:15-27. Furthermore, there is a genuine dispute between the expert witnesses who testified in this case regarding whether one skilled in the art in 1984 would understand that Dr. Lin's invention reached EPO produced in all mammalian hosts grown in culture. With respect to this dispute, the Court credits the testimony of Amgen's witnesses. On the first day of trial, Dr. Harvey Lodish explained that Example 10 "teaches that one can use vertebrate cells, mammalian cells in this process." Trial Tr. at 140:6-7. He continued, "[o]ne of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that we[re] used in this example, that other vertebrate cells, mammalian cells, could have been used." *Id.* at 140:7-11. After being asked to review other sections of the specification, Dr. Lodish explained that the Lin patent disclosed to those of ordinary skill in the art as of 1984 "that many types of vertebrate mammalian cells could be used" to produce EPO. *Id.* 251:3-12. He added definitively

that the "techniques described in the Lin patent are equally applicable to [mammalian] cells, other than COS or CHO cells, without question." *Id.* at 251:18-20. During an exchange with the Court, Dr. Lodish elaborated, explaining that one skilled in the art would infer from the examples using COS-1 and CHO cells that similar outcomes could be expected from other mammalian cells "[b]ecause these cells, vertebrate cells, mammalian cells specifically, make proteins and process them in substantially the same way." *Id.* at 141:16-18. Dr. Lodish did admit that "there may be minor differences, but those would be easy to figure out experimentally." *Id.* at 141:19-20. Thus, "with a strong likelihood of success, one could have used cells other than the CHO cells or the COS cells that he used in this patent." *Id.* at 141:20-23. Consistent with Dr. Lodish's testimony, Dr. Thomas Randolph Wall testified that the "teachings of the Lin patent describe vertebrate mammalian cells, and the techniques are all applicable to human cells which can be grown in culture." *Id.* at 2623:22-25. Consequently, the Court concludes that one of ordinary skill in the art in 1984 would have understood the teachings of the patent specification to encompass pharmaceutical compositions containing human erythropoietin purified from all mammalian cells grown in culture.

TKT's arguments that the Lin specification only teaches exogenous[49] EPO DNA expression systems and not endogenous EPO DNA expression systems does not alter this conclusion. While it is true that TKT put forth concrete documentary and testimonial evidence tending to show that Amgen's invention was limited to the expression of exo-

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[49] As previously explained, exogenous DNA is DNA that does not originate in the host cell into which it is inserted or transfected. Trial Tr. at 2619:18-19. It is DNA that has been removed from the cell in which it originated, placed in a vector, and reintroduced into a host cell. *Id.* at 1330:2-5.

genous DNA,[50] even if the Court were to assume that this point has been proven by clear and convincing evidence, this evidence would not earn TKT a finding of invalidity for lack

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[50] Dr. Kingston testified that the techniques that "are described in the Amgen patents consist of introducing expression vectors that encode exogenous EPO into COS cells or into CHO cells." Trial Tr. at 1321:1-4. Furthermore, Dr. Kingston opined that the Amgen patents do not describe the use of endogenous DNA to produce EPO protein. *Id.* at 1185:4-5; *see also id.* at 1186:6 to 1187:2. Experts called by both parties agreed (though some reluctantly) that the Amgen specification did not explicitly show any examples of human EPO production whereby the endogenous EPO DNA was expressed. *Id.* at 383:23 to 384:19, 1328:4-5, 1329:14 to 1330:1, 2659:11-13.

TKT also points to passages in the specification that tend to suggest that the patent was limited to the use of exogenous DNA: "These polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." Trial Ex. 1 at 10:15-20. This quotation lends substantial support to TKT's claim, for Amgen seems to be pigeonholing itself by using the terms "uniquely characterized by . . . expression . . . of exogenous DNA sequences . . . ." *Id.* Elsewhere, the patent specification states that "it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of 'exogenous' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host." *Id.* at 37:38-43. Certainly, one would expect the insertion of monkey origin DNA into human host cells in culture to be an instance of exogenous DNA expression because monkey DNA does not originate in the human genome. Yet it is noteworthy that Amgen apparently considered the insertion of monkey origin DNA into monkey host cells in culture as an instance of exogenous DNA expression as well. In order properly to consider such a technique exogenous, the monkey origin DNA would have to be isolated and then reintroduced into a monkey host cell. If, instead, Amgen were able to activate the monkey EPO DNA in the monkey cell, then the specification would presumably have described the technique as endogenous DNA expression. Thus, the implication to be drawn from this statement in the specification is that Amgen did not in fact contemplate applying its techniques to effectuate endogenous DNA expression.

of written description. TKT doctrinally misstates what the written description requirement demands of the patent applicant. When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise *after* the patent application is filed. *See United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1251 (Fed. Cir. 1989); *In re Koller*, 613 F.2d 819, 824-25 (Fed. Cir. 1980); *see also In re Hogan*, 559 F.2d 595, 606 (Ct. Cust. Pat. App. 1977). Instead, section 112 only requires the Court to determine whether the specification conveys to one of ordinary skill in the art as of 1984 that Dr. Lin invented the *subject matter* claimed in the patents-in-suit. *Reiffin,* 214 F.3d at 1346. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim—not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made. Thus, as long as the specification describes the invention referenced by a particular claim, it has met the written description requirement of section 112 even though it utterly fails to describe subsequent technology concerning the manner by which a claimed composition is manufactured.

Claim 1 of the '422 patent claims a product: a pharmaceutical composition. Trial Ex. at 38:39. As a result, whether endogenous or exogenous DNA expression is employed is immaterial and cannot be relied upon as a basis to render Claim 1 of the '422 patent invalid. Because Claim 1 of the '422 patent does not contain any limitations requiring endogenous gene-activation techniques using homologous recombination, the specification need not specifically describe such techniques. Thus, the Court finds that TKT has failed to prove by clear and convincing evidence that Amgen

failed to describe the invention claimed in Claim 1 of the '422 patent such that one of ordinary skill in the art in 1984 would know that Dr. Lin possessed the pharmaceutical composition claimed therein.

b. *'080 Patent*

The Court comes to the same conclusion with respect to Claims 2, 3, and 4 of the '080 patent. Claims 2 and 3 of the '080 patent claim isolated or non-naturally occurring erythropoietin glycoproteins having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6. Trial Ex. 3 at 38:39-50. Claim 4 covers pharmaceutical compositions comprising a therapeutically effective amount of the erythropoietin products according to Claims 2 or 3. *Id.* at 38:51-53.

Various passages of the specification describe all of the elements of these claims. The very first sentence of the "Brief Summary" section explains that "[t]he present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof." Trial Ex. 1 at 10:9-15; *see also id.* at 10:34-40, 10:50-60. The isolation and purification of expressed polypeptides is also referenced in the "Brief Summary" section as well as in the context of subsequent examples. *Id.* at 11:15-19. In addition, Figure 6 is described extensively in the specification and Figure 6 itself provides critical information regarding the sequence of erythropoietin amino acid residues necessary for the production of claimed EPO glycoproteins. *Id.* at 21:3-19; *see also id.* at 10:50-53. Furthermore, the specification contains complete and detailed

descriptions of the production of isolated and non-naturally occurring human EPO glycoproteins. *See id.* at 23:1 to 24:38 (Example 7); *id.* at 25:29 to 29:7 (Example 10). The patent also disclosed the in vivo biological effect of CHO-produced EPO upon hematocrit levels in mice. *Id.* at 28:13-28. The specification further describes the polypeptide products as:

> suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

Id. at 33:22-30.

Dr. Lodish identified these and other passages within the specification that "to me and to anyone else demonstrated unequivocally [that Dr. Lin] had done what he said he did . . . ." Trial Tr. at 527:11-12. In addition to the relevant portions of column 10 and Examples 7 and 10, Dr. Lodish also opined that "perhaps the most important thing would be the sequence of the EPO gene which he cloned and identified, the sequence of Figure 6 [b]ecause with that sequence in hand one has, as it were, the basic raw materials to use to make EPO as he described in many other ways." *Id.* at 527:19-23. With respect to the gene sequence, Dr. Lodish concluded:

> the gene sequence is an important part of the description because, simply put, with the correct gene sequence in hand, and he certainly had it to demonstrate it, I, as one skilled in the art, or my students or my post-docs, would know that by expressing this in many cells using various promoters one could make that EPO glycoprotein. It

would simply reinforce the other statements in the patent that he actually had it, yes.

Id. at 528:12-19. The Court credits Dr. Lodish's testimony regarding what one skilled in the art would know after reading Dr. Lin's specification regarding the EPO glycoproteins and the pharmaceutical compositions derived therefrom claimed in Claims 2, 3, and 4 of the '080 patent. Thus, after consideration of the documentary and testimonial evidence, the Court finds that TKT has failed to show by clear and convincing evidence that the asserted claims of the '080 patent were not sufficiently described by the specification.

In reaching this conclusion, the Court rejects the same arguments mentioned above that TKT pressed with respect to the '422 patent. In particular, the Court notes that the asserted claims of the '080 patent claim products: polypeptides and pharmaceutical compositions. These product claims are not limited by the processes by which they are made. Thus, the written description requirement does not necessitate that Dr. Lin explicitly describe every possible way in which his EPO polypeptide and pharmaceutical composition could be obtained. Instead, he was merely required to show to those skilled in the art in 1984 that he, in fact, had obtained these products. His specification meets this requirement.

c. *'349 Patent*

The asserted claims of the '349 patent claim recombinant, EPO-producing vertebrate cells and a process for producing erythropoietin comprising the step of culturing these cells under suitable nutrient conditions. Trial Ex. 5 at 38:8-14, 38:18-27, 38:31-36. Because the specification provides sufficient description of the claimed inventions to give notice to one of ordinary skill in the art as of 1984 that Dr. Lin actually possessed the inventions, TKT's written description attack fails here as well.

The specification announces in the "Brief Summary" section that:

> Vertebrate (e.g., COS-1 and CHO) cells provided by the present invention comprise the first cells ever available which can be propagated in vitro continuously and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U (preferably in excess of 500 U and most preferably in excess of 1,000 to 5,000 U) of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.

Trial Ex. 1 at 10:4249. Various passages of the specification go on to describe certain aspects of these EPO-producing cells. For example, the specification depicts in Figures 3 and 4 and describes extensively in Examples 6 and 7 the construction of vectors carrying transcription control DNA sequences and EPO DNA. *Id.* at 21:40 to 22:67 (Example 6); *id.* at 23:1 to 24:38 (Example 7). The specification also describes the role of promoter and regulator DNA sequences, *id.* at 2:3-8, and explains that the transcription control DNA sequences "which precede a selected gene (or series of genes) in a functional DNA polymer cooperate to determine whether the transcription (and eventual expression) of a gene will occur," *id.* at 2:10-13. Specifically, the patent identifies its SV40 late promoter as one type of non-human transcription control DNA sequence that an artisan might use to cause the expression of the EPO gene. *Id.* at 24:12-14. Additionally, Example 5 and Figure 6 provide one skilled in the art information regarding the primary structural conformation of human EPO, data which opened the floodgates to high level EPO production.

Furthermore, Example 10 provides a detailed description of the creation of these EPO-producing cells. *Id.* at 25:29 to 29:7. Example 10 instructs skilled artisans to transfect CHO DHFR$^-$ cells growing in media with the vectors earlier

identified in the patent and a mouse DHFR gene. *Id.* at 25:51-59. "Only those cells which have been stably transformed with the DHFR gene, and thereby the EPO gene, survive" when dispersed into media lacking hypoxanthine and thymidine. *Id.* at 25:63-65. The cells can then be propagated continuously in such media. *Id.* at 25:66 to 26:3. The patent then reports the units of human EPO obtained from the culture fluids from the transfected CHO cells. *Id.* at 26:11-18. The specification then describes how a skilled artisan might increase the level of EPO production by employing gene amplification techniques. *Id.* at 26:19-65. Giving rise to claims in the '349 patent that cover cells that produce EPO at specified levels, the specification reports that following gene amplification of the cells, "[t]he effective production rates for these culture conditions were thus 1264 and 2167 $U/10^6$ cells/48 hours." *Id.* at 26:63-65. The combination of these passages in the patent specification describes all of the elements of the asserted claims of the '349 patent.

Though the disclosures themselves provide significant evidence that the claims of the '349 patent are adequately described in the patent, the Court also credits the expert testimony bolstering this conclusion. With respect to Claims 1 and 4 of the '349 patent, Dr. Lodish specifically identified Figures 3, 4, and 6, lines 41 through 49 of column 10, and Examples 7 and 10 as sources of information in the patent that "would inform one of ordinary skill in the art as of 1984 that Dr. Lin possessed the vertebrate cells described" in independent Claims 1 and 4 of the '349 patent. Trial Tr. at 528:23 to 529:22, 530:6 to 531:8. Dr. Wall's testimony corroborates Dr. Lodish's opinion:

> Q. In your opinion, does the Lin patent specification, looking at the claims of the '349 patent, Claims 1 and 4, in particular, the independent claims, in your opinion, does the Lin patent specification describe the subject matter claimed in those claims?

A. Yes, it does.

Q. Where in the patent do you find the description . . . that supports the subject matters that's claimed in the claims of the '349 patent?

A. Vertebrate cells, which are described in Claim 1 and Claim 4, are summarized in Column 10, line 41 through 49. And then specific examples are also provided in Example 7, which refers to COS cell expression, and Example 10, which describes CHO cell expression, and the vectors which you use are those described in Figures 3 and 4 of the patent.

Id. at 2621:9-23; *see also id.* at 2614:7 to 2615:10; Trial Ex. 186(a) Tab 1 at 106. According to these experts, based on the disclosures contained in the patent, one skilled in the art in 1984 would have understood that Dr. Lin possessed vertebrate cells that could be propagated in vitro in culture, comprised non-human transcription control DNA sequences that controlled the transcription of DNA encoding human erythropoietin, and produced human erythropoietin at the levels recited in the claims of the '349 patent. *See id.* at 297:20 to 298:10, 528:23 to 531:8, 533:8 to 534:3, 2613:20 to 2614:6, 2621:9-23. In particular, the specification describes specific examples of cells containing DNA vectors that contain a non-human DNA transcription control sequence, the SV40 viral promoter enhancer, that is functional in vertebrate and mammalian cells. *See id.* at 126:15 to 127:14, 250:6-18, 253:13 to 254:11, 1201:5-8. Furthermore, it was a matter of common knowledge to one of ordinary skill in the art in 1984 that many different transcription control sequences could be used to make the claimed cells. *Id.* at 301:9 to 302:20, 1457:10-24. In light of this testimony and the extensive description contained in the specification, the Court finds that TKT has failed to prove by clear and convincing evidence

that the claims of the '349 patent are invalid for lack of written description.[51]

d. *'933 Patent*

Though the Court has earlier held that the asserted claims of the '933 patent are not infringed, solely for the purpose of providing a more complete record upon review, the Court now addresses whether any of those claims are invalid due to insufficient written description. Upon examination of the evidence, the Court finds that the specification, considered as a whole, fails to convey to one of ordinary skill in the art that Dr. Lin invented the subject matter claimed in the asserted claims of the '933 patent. *See Reiffin*, 214 F.3d at 1346; *see also Vas-Cath*, 935 F.2d at 1563. As a result, the Court finds that TKT has proven by clear and convincing evidence that these claims are invalid for lack of written description.

Claim 1 of the '933 patent claims non-naturally occurring erythropoietin glycoprotein products having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin. Trial Ex. 2 at 38:17-21. Dependent Claim 2 claims the product meeting the limitations of Claim 1 and requires that such product have a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE. *Id.* at 38:22-25. Lastly, dependent Claim 9 claims a pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy

[51] For the reasons explained with respect to the '422 patent, the Court again rejects not only TKT's argument that Dr. Lin failed adequately to describe human cells that met the additional limitations of the '349 claims, but also TKT's attempt to render the '349 patent invalid on the basis that it fails adequately to describe cells that express the endogenous human EPO gene.

according to Claims 1 or 2 and a pharmaceutically acceptable diluent, adjuvant, or carrier. *Id.* at 39:1-4.

Various portions of the disclosure refer to relevant aspects of these claims. As cited above with respect to the '080 patent, the first sentence of the "Brief Summary" section explains that:

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.

Trial Ex. 1 at 10:9-15; *see also id.* at 10:34-40, 10:50-60. Moreover, Dr. Lin disclosed a complete and detailed explanation of the production of non-naturally occurring human erythropoietin glycoproteins. *Id.* at 23:1 to 24:38 (Example 7); *id.* at 25:29 to 29:7 (Example 10). The patent also provides important data indicating that the glycoproteins have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. *Id.* at 28:13-28. Toward the end of the specification, Dr. Lin explained:

> to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C

> synthesis . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

Id. at 33:19-31. Furthermore, with respect to Claim 9, the specification describes nearly all of the limitations of the pharmaceutical composition claimed in the '933 patent. *Id.* at 12:1-7. In particular, Dr. Lin identified specific diluents, adjuvants, and carriers that could be utilized in the delivery of erythropoietin therapy. *Id.* at 33:61 to 34:27. In addition, other sections of the disclosure provide detailed information concerning effective dosages and therapeutic effectiveness. *Id.* at 28:16-27, 33:50-61. These passages provide highly relevant descriptions of nearly all of the limitations of the inventions claimed in the '933 patent. Furthermore, the Court relies upon the testimony of Dr. Lodish, cited above with respect to the glycoproteins claimed in the '080 patent, in finding that, as to each limitation but one, the information contained in the patent conveys to one of ordinary skill in the art that Dr. Lin invented the subject matter claimed in the asserted claims of the '933 patent. *See* Trial Tr. at 527:11-12, 527:19-23, 528:12-19.

Despite these findings favorable to Amgen, TKT persuades the Court by clear and convincing evidence that Dr. Lin's disclosure fails adequately to describe an EPO glycoprotein whose glycosylation differs from that of human urinary erythropoietin, and that this failure is fatal to all three of its asserted '933 claims. Considering the high burden of proof placed upon TKT, the question is admittedly close because Amgen has put on a spirited defense to TKT's charge of invalidity on this point.[52] But, as previously explained in the

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[52] In particular, Amgen (1) directed the Court's attention to numerous sections of the specification that discuss glycosylation and, more precisely, differences in glycosylation from that of human urinary erythropoietin; and (2) elicited testimony from Dr. Cummings concluding that one of ordinary skill in the art as of 1984 would understand that Dr. Lin's invention possessed a non-naturally occurring EPO glycoprotein whose

infringement portion of this opinion, the glycosylation of human urinary erythropoietin is a standardless standard. *See supra* Section IV.E.2, at 139-46. In summary, the documentary and testimonial evidence supporting this conclusion in the infringement context is incorporated here and reveals that (1) the glycosylation of urinary erythropoietin has "enormous heterogeneity"; (2) different purification techniques, several of which were known by one skilled in the art in 1984, result in differing glycosylated erythropoietin populations; (3) despite referring to at least two purification methods, the patent does not identify which human urinary erythropoietin preparation ought be used as a standard, nor would a skilled person know which urinary EPO preparation should be used; and (4) different urinary erythropoietin samples have different glycosylation. As a result, making comparisons between the glycosylation of recombinant EPO and that of human urinary EPO is virtually impossible. This is not to say, however, that such a comparison could not be accomplished as against a *particular* human urinary erythropoietin sample. Instead, the problem lies in the fact that Dr. Lin failed to disclose which of the varying urinary EPO preparations ought be utilized, and contrary to Dr. Cummings' testimony, the Court finds that one of ordinary skill in the art as of 1984 would not be able to guess the appropriate EPO preparation. As a result, the patent fails to convey to one of ordinary skill in the art as of 1984 that Dr. Lin invented an erythropoietin glycoprotein product having glycosylation which differs from that of human urinary erythropoietin. Thus, despite sufficient written description of each of the limitations contained in the three asserted claims of the '933

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glycosylation differed from that of human urinary EPO. *See* Trial Ex. 1 at 5:48-53, 10:28-41, 28:33 to 29:7, Fig.6 (noting asparagine-linked glycosylation by asterisk); Trial Tr. at 569:16-24, 570:20 to 571:2, 607:22 to 614:3, 619:21 to 620:5, 620:13 to 627:12, 653:5 to 654:8, 659:15 to 660:19.

patent save one, if the finding of non-infringement were to be ruled error, this Court would, in the alternative, rule that all three[53] asserted claims of the '933 patent are invalid for lack of written description.[54]

3. *Definiteness*

The Court holds that despite meeting the other limitations of the asserted '933 claims, HMR4396 does not infringe the limitation that the erythropoietin glycoprotein product have "glycosylation which differs from that of human urinary erythropoietin." Nonetheless, the Court now addresses TKT's alternative defense regarding this claim limitation, i.e., that human urinary erythropoietin is indefinite.

According to the relevant statute, "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112. "Determining whether a claim is definite requires an analysis of 'whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.'" *Personalized Media Communications, LLC* v. *Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998) (quoting *Miles Lab., Inc.* v. *Shandon, Inc.*, 997 F.2d 870, 875 [Fed. Cir. 1993]); *see also Space Sys./Loral, Inc.* v. *Lockheed*

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[53] The Court's ruling applies to all three claims because the limitation that the erythropoietin glycoprotein product have glycosylation which differs from that of human urinary erythropoietin is contained in Claim 1 and is required, by dependency, in Claims 2 and 9. Trial Ex. 2 at 38:20-21, 38:23, 39:3.

[54] As should be abundantly clear by this point, in reaching this conclusion, the Court was not persuaded by TKT's alternative arguments that Amgen failed adequately to describe the production of erythropoietin either by use of a human cell line or by activating the otherwise dormant endogenous erythropoietin gene. *See supra* note 51.

Martin Corp., Nos. 99-1255, 99-1289, 2000 WL 1205154, at *10 (Fed. Cir. Aug. 23, 2000) (unpublished opinion); *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1217-18 (Fed. Cir. 1991). The focus of the inquiry, then, is on the clarity of the claim terms and the extent to which such terms, viewed from the perspective of one of ordinary skill in the art, sufficiently identify the actual invention. Relating as it does to the Court's performance of its duty to construe the claims, the indefiniteness determination is made as matter of law. *Personalized Media*, 161 F.3d at 705.

As explained in the '933 patent infringement and adequate written description portions of this opinion, *see supra* Section IV.E.2, at 139-46; *supra* Section IV.F.2.d, at 214-16, the term "gylcosylation of human urinary EPO" does not have a precise meaning. Although the language contemplates that a competitor concerned with infringing the '933 patent can empirically determine whether its product's glycosylation differs from the glycosylation of human urinary erythropoietin, a definitive comparison is rendered impossible by the fact that human urinary erythropoietin itself varies significantly. This is not the kind of particular pointing out and distinct claiming that is required by the statute. 35 U.S.C. § 112. Consequently, despite appearing to be "definite," the term actually lacks sufficient clarity to place those of ordinary skill in the art on notice of the bounds of the invention.

Here, the Court incorporates the factual findings, which are summarized above on page 215, *see supra* Section IV.E.2, at 13946; *supra* Section IV.F.2.d, at 214-16, underlying the determination that HMR4396 does not infringe this claim limitation of the '933 patent. As summarized by Drs. Paul T. Matsudaira and Phillips W. Robbins, because different urinary erythropoietin preparations vary in their glycosylation, and because neither the patent nor the prior art provides clear guidance as to which human urinary EPO standard ought be used, one of ordinary skill in the art would be unable to

determine whether a particular erythropoietin has gylcosylation which differs from that of human urinary erythropoietin. Trial Tr. at 1845:13 to 1846:25, 1979:7 to 1980:11, 2314:7-23. The Court relies upon these findings in holding that the term "human urinary erythropoietin" is indefinite. Because the claim term fails to apprise those skilled in the art of the scope of the invention, TKT has proved by clear and convincing evidence that the claim is indefinite, and if upon review, the finding of non-infringement is error, the Court so rules.

4. *Enablement*

At various points throughout this litigation—from the *Markman* hearing right through to the final argument—the Court noted that the issue of enablement would perhaps be the critical area of the contest. Recognizing as much, both parties deployed substantial squadrons to this theater, and the battle raged. After much reflection, the Court finds that Amgen survives, albeit barely.

Like the written description requirement, the statutory basis for the enablement inquiry is section 112, which states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112. The Federal Circuit has elaborated: "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc.* v. *Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 [Fed. Cir. 1993]); *see also In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The disclosure meets the enablement requirement even if a "rea-

sonable" amount of routine experimentation is necessary in order to practice a claimed invention, as long as such ex perimentation is not "undue." *Enzo Biochem, Inc.* v. *Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999); *In re Wands,* 858 F.2d 731, 736-37 (Fed. Cir. 1988). In determining whether the necessary experimentation would be "undue," the Federal Circuit has set forth the following factors to guide the inquiry:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d at 737. Whether claims are sufficiently enabled by the specification is determined as of the filing date of the patent application. *Enzo Biochem*, 188 F.3d at 1371; *Hybritech, Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). Thus, the court makes an enablement determination "retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time." *Enzo Biochem*, 188 F.3d at 1371-72 (citing *Hybritech*, 802 F.2d at 1384; and *Wright,* 999 F.2d at 1562-63). This determination is made as matter of law, though the legal conclusion rests upon findings of fact. *Nat'l Recovery Tech., Inc.* v. *Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999). Moreover, proof of invalidity due to lack of enablement must be clear and convincing, for the presumption of validity includes a presumption that the patent complies with section 112. *See* 35 U.S.C. § 282; *Nat'l Recovery*, 166 F.3d at 1195 (citing *Northern Telecom, Inc.* v. *Datapoint Corp.*, 908 F.2d 931, 941 [Fed. Cir. 1990]). The burden, then, falls squarely upon TKT clearly and con-

vincingly to persuade the Court that Amgen's claims are invalid because they are not enabled.

a. *'422 Patent*

Claim 1 of the '422 patent claims a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin, which is purified from mammalian cells grown in culture, and a pharmaceutically acceptable diluent, adjuvant or carrier. Trial Ex. 6 at 38:37-41. In light of the legal framework, the Court's duty is to determine whether the specification of Dr. Lin's patents teaches those skilled in the art how to make and use the full scope of the claimed pharmaceutical composition without undue experimentation. *Enzo Biochem*, 188 F.3d at 1371-72.

First, to the extent that such findings are relevant here, the Court incorporates the numerous factual findings regarding the sufficiency of Dr. Lin's disclosure that undergird the Court's finding that Claim 1 of the '422 patent is not invalid due to inadequate written description. *See supra* Section IV.F.2.a, at 203-07. Dr. Lin's disclosure provides ample information teaching those skilled in the art how to manipulate certain cells genetically so that they produce human erythropoietin. *See, e.g.*, Trial Ex. 1 at 25:29 to 29:7 (Example 10); *id.* at Fig.6; Trial Tr. at 125:13-24. In addition, though the Court notes that many purification techniques were already well-known in the art as of 1984, *see* Trial Exs. 42, 2012, 2233, 2235-36, 2247, 2252, 2333, 2440; Trial Tr. at 632:13 to 634:1, 1846:19-22, 1970:6 to 1979:8, 2189:16 to 2190:25, 2193:9 to 2194:15, 2197:2-19, the specification described how to purify human erythropoietin from certain mammalian cells grown in culture. Trial Ex. 1 at 11:15-19, 28:28-32; Trial Tr. at 1631:21 to 1632:6, 1982:24 to 1983:17. The specification also teaches skilled artisans how to prepare and use pharmaceutical compositions containing therapeutically effective amounts of human erythropoietin. Trial Ex. 1 at 12:1-7, 33:50 to 34:27; Trial Tr. at 125:13-24, 137:5-

11, 264:4 to 265:24, 1336:18-20. Thus, at least with respect to the limitations of Claim 1 concerning both the purification and the therapeutically effective use of the erythropoietin product, between what those skilled in the art already knew and what Dr. Lin disclosed to the world in the specification, a skilled artisan would be enabled to make and use the claimed pharmaceutical composition. The question remains, however, whether the specification enables one of ordinary skill in the art to practice the invention using *all* cultured mammalian cells—this is the scope of the claim. Put differently, in light of the breadth of the disclosure, should Amgen's claims have been limited to a smaller subset of cell types?

Dr. Lin's disclosure provides only two examples of mammalian cells that produce erythropoietin. Trial Ex. 1 at 23:1 to 24:38 (Example 7, using COS-1 cells); *id.* at 25:29 to 29:7 (Example 10, using CHO cells). The question then arises whether the explicit disclosure of just two mammalian cell lines warrants a claim covering all mammalian cells. Rather than properly seeking a claim equal in measure to the scope of the disclosure, it appears that Dr. Lin claimed far more than what he delivered. This is exactly the type of conduct that the enablement requirement is intended to smoke out. But a claim should not be squeezed uncomfortably into the dinghy of a particular example, if the teachings of the patent warrant the capacious comfort of an ocean liner. TKT, of course, argues that the teachings simply are not so broad.

True, Drs. Lodish and Wall testified that one of ordinary skill in the art in 1984 could have practiced the Lin inventions in a variety of different mammalian cell types with routine experimentation. Trial Tr. at 137:21 to 142:1, 251:6 to 253:9, 2605:9 to 2606:1, 2608:19 to 2609:16; 2674:8 to 2676:6, 2677:24 to 2678:25. As already mentioned with respect to the written description requirement, Dr. Lodish explained that Example 10 "teaches that one can use vertebrate cells, mammalian cells in this process," *id.* at 140:6-7, and that

"[o]ne of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that we[re] used in this example, that other vertebrate cells, mammalian cells, could have been used," *id.* at 140:7-11. *See also id.* at 251:3-12 (discussing additional sections of the specification).[55] He then confidently added that the "techniques described in the Lin patent are equally applicable to [mammalian] cells, other than COS or CHO cells, without question." *Id.* at 251:18-20. During an exchange with the Court, Dr. Lodish elaborated on his reasoning. He explained that one of ordinary skill in the art would infer from the examples using COS-1 and CHO cells that similar outcomes could be expected from other mammalian cells "[b]ecause these cells, vertebrate cells, mammalian cells specifically, make proteins and process them in substantially the same way." *Id.* at 141:16-18. All mammalian cells produce and secrete hormones like EPO by means of the same fundamental process of gene transcription, RNA splicing, mRNA translation, and post-translational modification. *Id.* at 83:6 to 88:13, 120:9-22, 141:15-20; *see also id.* at 2550:7-15, 2580:18-22. Dr. Lodish did admit that "there may be minor differences, but those would be easy to figure out experimentally." *Id.* at 141:19-20. Thus, "with a strong likelihood of success, one could have used cells other than the CHO cells or the COS cells that [Lin] used in this patent." *Id.* at 141:20-23; *see also id.* at 542:25 to 543:7, 2605:9 to 2606:1. Furthermore, there is no evidence in the record indicating that human cells are somehow different from other mammalian cells and would, therefore, be unsuitable for producing erythropoietin following Dr. Lin's teachings. *Id.* at

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[55] The Court also notes that by 1984, a variety of mammalian cells useful for protein expression had been adapted for growth in culture and were readily available to those of ordinary skill in the art from the American Type Culture Collection ("ATCC"). Trial Tr. at 2678:17 to 2679:5, 2685:24 to 2686:19. A number of cultured human cell lines were available as well. *Id.* at 252:19 to 253:3, 1209:19-21, 2616:2-12.

2556:5-13. Consistent with Dr. Lodish's testimony, Dr. Wall testified that the "teachings of the Lin patent describe vertebrate mammalian cells, and the techniques are all applicable to human cells which can be grown in culture." *Id.* at 2623:2225. When pressed regarding the difficulty of identifying suitable expression systems for making erythropoietin, for instance, Dr. Wall and his interrogator had the following exchange:

> Q. [Y]ou would have to determine whether . . . there were suitable expression systems for making EPO in those cells? Is that correct?
>
> A. [Y]ou wouldn't need to design an expression system, that there were already available broadly active, that is, with a broad spectra of host cell specificity or activity many suitable vectors.
>
> Q. And you need to find out whether the particular host cell you were looking at possessed a suitable system, correct?
>
> A. It would be a routine experiment to test one of the readily available SV40 or mouse metallothionein or whatever other expression system you wanted to try.

Id. at 2674:19 to 2675:9. Throughout the testimony of these witnesses, a theme becomes apparent: any challenge which one of ordinary skill in 1984 might have encountered in attempting to make and use the claimed invention using other cultured mammalian cells could be resolved by experimentation falling short of "undue." As the Court finds this testimony credible, it cannot find by clear and convincing evidence that after reasonable experimentation one skilled in the art as of 1984 would not have been able to make and use a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin purified from mammalian cells grown in culture.

Another issue merits consideration, however. Throughout this litigation, TKT has made every effort to point out the fact

that whereas Amgen recombines exogenous EPO DNA sequences, TKT activates the endogenous EPO gene. As previously mentioned, TKT attempted to insert an exogenous DNA limitation somewhere within nearly every asserted claim. Then and now, the Court maintained that the claim language could not reasonably be read to incorporate such a limitation. Instead, the Court opined that if the exogenous-endogenous dispute belonged anywhere in this case, it ought be faced in the context of the validity arguments. Well, here it is.

As an initial matter, TKT's contention must be clarified. Taking the Court's claim construction as issued, TKT notes (as it must) that the claimed pharmaceutical composition is not defined by the EPO gene's relationship to its host. Having lost that battle during the *Markman* hearing, TKT now comes about and argues, essentially, that "if the claim construction is that broad, then Amgen's disclosure better meet it." Fair enough.

TKT is correct that HMR4396 Injection is produced by activating the endogenous EPO gene and that, in contrast, all of Dr. Lin's specific examples are devoted to the insertion of exogenous EPO DNA into host cells. As earlier detailed with respect to the written description analysis of the '422 patent, TKT's evidence tends to show that Amgen's invention was limited to the expression of exogenous DNA. *See supra* note 50. While the Court is willing to assume that this contention has been proven by clear and convincing evidence, a finding of invalidity for lack of enablement does not follow. Like the written description requirement, *see supra* Section IV.F.2.a, at 200-03, where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed. *See United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247,

1251 (Fed. Cir. 1989); *In re Koller*, 613 F.2d 819, 824-25 (Ct. Cust. Pat. App. 1980); *see also In re Hogan*, 559 F.2d 595, 606 (Ct. Cust. Pat. App. 1977). Moreover, the law makes clear that the specification need teach only one mode of making and using a claimed composition. *See Johns Hopkins Univ.* v. *Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998); *Engel Indus. Inc.* v. *Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991). As a result, contrary to what TKT proposes here, there is no requirement that the specification enable every mode for making and using the claimed products.[56] Thus, the facts that (1) TKT makes the same pharmaceutical composition but by a different method; and (2) that such method is not taught in the Amgen patent, are wholly immaterial. As a result, because the record is replete with persuasive evidence that Dr. Lin's disclosure taught those skilled in the art at least one method of making and using the pharmaceutical composition of Claim 1 of the '422 patent, the specification is sufficient to overcome this enablement challenge.

b. *'080 patent*

Claims 2 and 3 of the '080 patent claim erythropoietin glycoproteins having certain characteristics, and Claim 4 claims a pharmaceutical composition comprising a therapeutically effective amount of the erythropoietin products according to Claim 2 or 3. Trial Ex. 3 at 38:39-53. Dr. Lin's

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[56] The reason for such a rule is clear. What would be the value in patenting a composition at all if, by making the slightest alteration in the method of making what is nonetheless the same product, a competitor were able to evade liability? A patent system that permitted such conduct would remove the carrot dangling in front of the inventor's nose. If inventors were so easily divested of their limited monopoly rights attendant to their novel, useful, and nonobvious contributions, they would likely abandon their pursuits and thereby inhibit progress. The law does not permit such an outcome.

disclosure enables those skilled in the art as of 1984 to practice these inventions.

In reaching this conclusion, the Court incorporates within its analysis the evidentiary foundation relied upon to find that the '080 claims did not run afoul of the written description requirement. *See supra* Section IV.F.2.b, at 203-07. In summary, the text and figures of the specification describe the isolation and purification of the claimed erythropoietin polypeptides in such a manner as to enable one skilled in the art to make and use these polypeptides as well as pharmaceutical compositions containing them. *See, e.g.*, Trial Ex. 1 at 10:9-15, 10:34-40, 10:50-60, 11:15-19, 21:3-19, 23:1 to 24:38 (Example 7), 25:29 to 29:7 (Example 10), 31:13-54, 32:44-60, 33:19-30, 35:10-17, Fig.6; Trial Tr. at 527:19-23, 528:12-19. Even Dr. Kingston, who was called by TKT, agreed that if one of ordinary skill in the art as of 1984 followed Example 10, then such person would be able to make an erythropoietin polypeptide in CHO cells. Trial Tr. at 2110:6-10. Neither he, nor any other witness, claimed that the specification's examples were inoperable. *Id.* at 2109:20-25. Furthermore, to the extent that a skilled artisan would be led astray by the erroneous Hexose value or the additional arginine at position 166 of the deduced amino acid chain displayed in Figure 6, both discrepancies were discoverable through reasonable experimentation. As a result, these scientific errors do not render any of the asserted claims invalid for lack of enablement.

TKT argues that the asserted '080 patent claims are invalid because the Lin patent specification does not enable one skilled in the art to produce erythropoietin glycoproteins (and pharmaceutical compositions) by activating the endogenous EPO gene in a human cell. As previously explained, however, this unique method by which TKT achieves the same outcome need not be enabled provided that the patentee teaches a skilled artisan at least one method of obtaining a

claimed composition. *See supra* Section IV.F.4.a, at 228-30. Furthermore, whereas the scope of Claim 1 of the '422 patent, which recites "mammalian cells," reaches a broad range of host cells capable of expressing the human EPO gene, the asserted claims of the '080 patent do not. Thus, TKT's argument that the specification fails to enable the production of EPO using cells other than CHO cells (including human cells) is inapposite. Thus, the Court finds that one of ordinary skill in the art would have been able to make and use the claimed erythropoietin glycoproteins and the pharmaceutical composition containing them.

c. *'349 Patent*

As to the asserted claims of the '349 patent, the Court also concludes that the written description, when combined with the knowledge of those of ordinary skill in the art as of 1984, teaches skilled artisans how to make and use the claimed unique vertebrate cells. In analyzing TKT's written description challenges to the '349 patent, the Court considered various passages from the specification as well as helpful testimony from the witnesses. Much the same evidence undergirds the Court's enablement holding. *See supra* Section IV.F.2.c, at 207-11.

In sum, various passages of the specification provide important data regarding, for instance, promoter and regulator DNA sequences, the creation of vectors carrying transcription control DNA sequences and human EPO DNA, the primary structural conformation of human EPO, selection and amplification techniques, and methods to quantify the erythropoietin production rates of the cells. *See, e.g.*, Trial Ex. 1 at 2:3-8, 2:10-13, 10:42-49, 21:40 to 22:67 (Example 6), 23:1 to 24:38 (Example 7), 25:29 to 29:7 (Example 10), Fig.6. Moreover, the art was already rich in certain aspects of these teachings. For example, as of 1984, ordinary skilled artisans had identified a variety of promoters that could be used to promote gene expression in a variety of mammalian and

vertebrate cells. Trial Tr. at 301:12 to 302:4, 302:23 to 303:2. Determining whether a given promoter would operate within a particular cell type was a matter of routine experimentation. *Id.* at 302:5-20. One skilled in the art at that time also would have understood that a variety of vertebrate cells adapted for growth in culture could be obtained from the ATCC. *Id.* at 2678:17 to 2679:5, 2685:24 to 2686:19. In addition, a number of cultured human cell lines were available. *Id.* at 252:19 to 253:3, 1209:19-21, 2626:2-12. One skilled in the art of molecular biology would have understood that because all vertebrate cells produce and secrete hormones by the same fundamental processes, the teachings displayed in the '349 patent were readily applicable to the entire range of cultured vertebrate cells, including human cells. *Id.* at 83:6 to 88:13, 120:9-22, 141:15-20, 2550:7-15, 2556:5-13, 2580:18-22. These aspects relating to the Lin patents were already well known in the art prior to Dr. Lin's disclosure.

Building on this art, Dr. Lin's disclosure taught ordinary skilled artisans how to practice the claimed vertebrate cell inventions. *Id.* at 254:12 to 255:23. In particular, the teachings enabled one of ordinary skill in the art to use various cultured vertebrate and mammalian cells, including human cells, to produce human EPO. *Id.* at 123:12-22, 137:21 to 138:1, 140:6 to 142:1, 250:3 to 253:12, 541:15 to 543:10, 627:21 to 629:4, 1112:16 to 1113:11, 1124:23 to 1125:2, 2109:20 to 2110:21, 2554:21 to 2555:3, 2556:11-13, 2580:11-25. With the assistance of the Amgen specification, a skilled artisan would have been able to determine with routine experimentation which cultured vertebrate cells would produce human EPO. *See id.* at 137:21 to 138:12, 139:8-20, 140:6 to 142:1, 534:10 to 536:9, 2679:17 to 2679:5, 2685:24 to 2686:19. The same is true with respect to whether certain of the various promoters could be operatively linked to control the transcription of the DNA encoding human EPO. *See id.* at 514:22 to 515:5. The specification teaches how to use cultured vertebrate cells to make cells that contain non-

human DNA sequences that control transcription of human EPO DNA and, upon growth in culture, are capable of producing EPO at the levels recited in the claims. *Id.* at 254:1-23, 2605:9-20, 2605:22 to 2606:1. Among the many techniques described in the '349 patent for obtaining such cells are the use of (1) strong non-human promoters and enhancers; (2) selectable markers for isolation of cells capable of stable EPO expression in culture; (3) amplified markers for selection of cells containing amplified copies of EPO DNA under the control of non-human transcription control sequences; and (4) cell cloning. *Id.* at 2581:15 to 2582:3, 2599:15 to 2600:18, 2601:18 to 2603:25, 2604:13 to 2605:1. The patent also enables one of ordinary skill in the art to isolate EPO from EPO-producing cells and to measure such EPO. *Id.* at 378:12-23.

The extent of the enabling disclosure is also demonstrated by a series of post-filing publications that describe the creation of EPO-producing cultured human, monkey, and hamster cells using the techniques taught in the Amgen specification. *See Gould* v. *Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987) (explaining that an expert may rely upon post-filing publications that apply known techniques as of the filing date to show that the specification was enabling). Yanagi, for example, applied the teachings of the '349 patent to make cultured human cells capable of producing the claimed amounts of human EPO. *See* Trial Ex. 43; Trial Tr. at 2104:2-8, 2105:8-19, 2606:2 to 2607:13, 2608:7-13. Powell, similarly, made $DHFR^+$, COS, and BHK (baby hamster kidney) cells containing amplified human EPO DNA under the control of non-human transcription control sequences that were capable of producing human EPO at the levels recited in the '349 claims. *See* Trial Ex. 2323; Trial Tr. at 2609:11-16, 2609:24 to 2610:25. Ohashi, meanwhile, made EPO-producing $DHFR^+$ human cells that contained amplified human EPO DNA under the control of non-human transcription control sequences. Trial Tr. at 2612:20 to 2613:17. The fact that these re-

searchers were capable of making EPO-producing cells using non-human transcription control sequences and either amplified or non-amplified EPO DNA in various types of cultured cells including human cells further suggests that Amgen's specification was enabling. *Id.* at 2607:19 to 2608:1, 2608:19 to 2609:1.

The Court also notes that TKT failed to prove—at least by clear and convincing evidence—that one of ordinary skill in 1984 would not have been able to make and use vertebrate cells having the properties of Dr. Lin's claimed cells without undue experimentation. More precisely, TKT has failed to provide clear and convincing evidence that any person was unable to make and use the inventions claimed in the '349 patent in any vertebrate cell. In fact, Dr. Kingston, TKT's expert, conceded that a post-doctoral fellow working in his laboratory in 1984, applying the techniques described in the '349 patent, would have been able to make cultured human cells capable of expressing human EPO. *Id.* at 2111:13 to 2112:4, 2113:6-16.

TKT points to a portion of the prosecution history of the '349 patent in order to support its non-enablement contentions. During the prosecution of the '349 patent claims, Examiner Martinell rejected certain claims under 35 U.S.C. § 112 and stated that "[t]he instant application teaches and enables only cells that have been transformed with exogenous DNA that encodes erythropoietin (EPO) that have the high EPO production required by the claims." Trial Ex. 5 Tab 10 at 204. Although TKT argues that this snippet limits Amgen's cell claims to cells that have been transfected with exogenous EPO DNA, read in context, it does not support TKT's argument. The claim to which Examiner Martinell referred in the rejection was then pending Claim 42: "Vertebrate cells which can be propagated in vitro and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in

48 hours as determined by radioimmunoassay." *Id.* at 171. Thus, rejected Claim 42 literally encompassed vertebrate cells that had not been genetically manipulated at all—with endogenous *or* exogenous DNA—but were nonetheless capable of producing the recited levels of human EPO. In light of the originally filed claim, one must examine not only TKT's oft-quoted sentence of the rejection but also the statement that followed it: "[t]he instant application does not guide one of skill in the art in the discovery of *non-transformed vertebrate cells* that are capable of the high EPO production recited in the instant claims." *Id.* at 204 (emphasis added). Moreover, in support of his rejection, Examiner Martinell cited three publications, all of which described human cells that had not been genetically manipulated that produced EPO at levels far below the levels recited in the claims. *See id.* In light of this additional sentence and the cited publications, it becomes clear that Examiner Martinell was not concerned about limiting the claims so that genetic manipulation was endogenous rather than exogenous; rather, he was concerned about limiting the cell claims generally to transformed, or genetically manipulated, rather than non-transformed vertebrate cells. This conclusion is solidified by Amgen's submitted amended claims which, rather than limiting the claimed invention to cells comprising exogenous DNA encoding human EPO, limited the cell claims by adding limitations concerning genetic manipulation. In particular, the amended claims, which were later issued as Claims 1 and 4 of the '349 patent, were limited to vertebrate cells "comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin" or "which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences," respectively. *Id.* at 235, 242. Examiner Martinell agreed that the amended claims overcame his enablement rejection and consequently withdrew the section 112 rejection and allowed the amended claims to issue. *Id.* at 235, 255. It stands to reason that if he were objecting on the

basis that the Lin patents only enabled the manufacture of EPO-producing cells by using exogenous EPO DNA, then the enablement rejection would not have been withdrawn. Thus, the Court is not persuaded by clear and convincing evidence that Amgen's specification fails to enable ordinary skilled artisans to make vertebrate cells meeting all of the limitations of the '349 patent claims.[57]

TKT also points to Amgen's human '293 cell experiments as evidence that the '349 patent is not enabling. *See generally* Trial Ex. 2092 (Laboratory Notebook issued to J. Egrie). TKT contends that Dr. Lin should not have claimed classes of EPO-producing cells as broad as "mammalian" or "vertebrate" because these human '293 cell experiments failed to produce EPO in sufficient amounts.

The Court agrees that these experiments demonstrate levels of EPO production falling far short of the magnitude encompassed by the '349 claims. Moreover, the Court agrees that these experiments strongly suggest that such high level expression could not be obtained from this human cell line, at least by means of techniques known to those skilled in the art in 1984.

The '293 experiments, however, occurred months before Dr. Lin first disclosed his vertebrate cell inventions in the '349 patent. More importantly, as indicated above, *see supra* Section IV.F.1.c, at 189-90, the '293 experiments were not performed for the purpose of yielding high levels of EPO expression, Trial Tr. at 2556:13-16. Instead, they were transient expression experiments designed to achieve fast but

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[57] Because Amgen is only required to enable skilled artisans to make its claimed product by one method, the Court again rejects TKT's argument that the '349 patent claims are invalid because they fail to enable one of ordinary skill in the art to manufacture cells capable of expressing EPO from endogenous EPO DNA. *See supra* Section IV.F.4.a, at 227-30.

short-term expression of the EPO gene sequence cloned by Dr. Lin rather than stable transformants capable of high level EPO production. *Id.* at 428:10 to 429:12, 967:3-18, 1112:16 to 1113:11, 2111:19 to 2112:4, 2556:25 to 2557:8, 2559:1-6, 2568:9 to 2569:8, 2572:22 to 2573:4. Specifically, these experiments were designed to confirm that Dr. Lin had cloned an intact, complete DNA sequence encoding human EPO, *see id.* at 2568:11-23, and they did not employ the various techniques later described in Example 10 to increase EPO production levels. The '293 experiments, for example, did not include the use of (1) a strong promoter; (2) a selectable marker to allow selection of stable transformants; (3) an amplifiable marker to allow amplification of the EPO DNA; and (4) the use of sub-cloning to isolate homogeneous populations of high producing cell clones. *Id.* at 2569:16 to 2572:21, 2575:15 to 2577:23. Thus, while it appears that Amgen failed to obtain high level EPO expression in a human cell line, which directly challenges the patent's scope of enablement, Amgen was not attempting to apply all of the teachings of the '349 patent in those experiments. As a result, while the '293 experiments prove more likely than not that Amgen's '349 patents are not enabled, this Court does not find such proof clear and convincing.

d. *'933 Patent*

Although the Court has found that HMR4396 does not infringe the asserted claims of the '933 patent, the Court here addresses whether any of those three claims survive TKT's enablement onslaught. Claim 1 of the '933 patent covers non-naturally occurring erythropoietin glycoprotein products having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin. Trial Ex. 2 at 38:17-21. Dependent Claim 2 also requires that such product have a higher molecular weight than human urinary erythropoietin as

measured by SDS-PAGE. *Id.* at 38:22-25. Dependent Claim 9, meanwhile, covers pharmaceutical compositions comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to Claims 1 or 2 and a pharmaceutically acceptable diluent, adjuvant, or carrier. *Id.* at 39:1-4. The limitations contained in these claims are widely described throughout the specification, as is apparent from the extensive evidence cited by the Court with respect to the sufficiency of the written description of the '933 patent. *See supra* Section IV.F.2.d, at 211-16. For example, the specification discusses novel purified and isolated polypeptide products having part or all of the primary structural conformation and one or more of the biological properties of naturally-occurring erythropoietin, and provides a detailed explanation of the production of such erythropoietin glycoprotein products. Trial Ex. 1 at 10:9-15, 10:34-40, 10:50-60, 23:1 to 24:38 (Example 7), 25:29 to 29:7 (Example 10). In conjunction with disclosures concerning in vivo biological activity, therapeutic effectiveness, and other aspects of the '933 claims, these passages nearly enable one of ordinary skill in the art to practice the inventions claimed in the '933 patent. *Id.* at 12:17, 28:13-28, 33:19-31, 33:50 to 34:27; Trial Tr. at 625:11 to 629:11, 656:2 to 661:4.

Despite these enabling disclosures, Dr. Lin's specification falters, which by this point should come as no surprise to the reader, because it fails to enable one of ordinary skill in the art to compare the glycoyslation of the recombinant EPO product with that of human urinary erythropoietin. The Court directs the reader to more extensive discussions of this matter contained in the infringement, *see supra* Section IV.E.2, at 139-46, adequate written description, *see supra* Section IV.F.2.d, at 214-16, and definiteness, *see supra* Section IV.F.3, at 218-19, portions of this opinion. Consequently, an ordinary skilled worker would be unable to perform the experimental analysis necessary to confirm whether the manufactured glycoprotein product has glycosylation which

differs from that of human urinary erythropoietin. The Court therefore concludes, should the finding of non-infringement prove erroneous, that TKT has proven by clear and convincing evidence that the '933 patent specification does not enable one of ordinary skill in the art to make and use the erythropoietin glycoprotein product (and related pharmaceutical composition) encompassed within the three asserted claims of the '933 patent.

V. CONCLUSION, DECLARATION, AND ORDER FOR JUDGMENT

As this opinion comes to its conclusion, it is appropriate to reiterate that it truly has been an honor to have presided over a case litigated with such skill, intelligence, and integrity. The attorneys representing both parties have done an extraordinary job in teaching the Court many of the nuances of both this challenging area of law and this rather complicated realm of science. Litigation, however, is a rather rough-edged zero-sum enterprise. Accordingly—

For the reasons set forth above, the Court declares:

> Claims 1, 2, and 9 of the '933 patent are not infringed, and, if this finding is error, those claims are invalid for lack of an adequate written description, indefiniteness, and lack of enablement.
>
> Claims 4 through 9 of the '698 patent are not infringed.
>
> Claims 2 through 4 of the '080 are valid, enforceable, and infringed under the doctrine of equivalents.
>
> Claims 1, 3, 4, and 6 of the '349 patent are valid, enforceable, and literally infringed, whereas Claim 7 of the same patent is not infringed.
>
> Claim 1 of the '422 patent is valid, enforceable, and literally infringed.

An appendix follows, setting forth the Court's holding in tabular form.

Judgment will enter so declaring.

/s/ William G. Young
WILLIAM G. YOUNG
CHIEF JUDGE

APPENDIX[58]

	'933 Patent			'698 Patent	'080 Patent	'349 Patent					'422 Patent
	Claim 1	Claim 2	Claim 9	Claims 4-9	Claims 2-4	Claim 1	Claim 3	Claim 4	Claim 6	Claim 7	Claim 1
Literally Infringed?	no	no	no	no	no	yes	yes	yes	yes	no	yes[59]
Infringed by Doctrine of Equivalents?	no	no	no	no	yes		yes[60]		yes[60]	no	
Anticipated?	no	no	no		no	no	no	no	no		no
Obvious?	no	no	no		no	no	no	no	no		no
Inequitable Conduct?	no	no	no		no	no	no	no	no		no
Adequate Written Description?	no[63]	no[63]	no[63]		yes	yes	yes	yes	yes		yes
Definite?	no[60]	no[63]	no[60]								
Enabled?	no[60]	no[63]	no[60]		yes	yes[61]	yes[61]	yes[61]	yes[61]		yes
Final Result	not infringed	not infringed	not infringed	not infringed	valid and infringed	valid and infringed	valid and infringed	valid and infringed	valid and infringed	not infringed	valid and infringed

[58]Where an issue is left blank, it has been rendered moot by the infringement analysis or has not been raised by the parties.

[59]Ruling on summary judgment record.

[60]Dicta.

[61]Albeit barely.

APPENDIX F

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

05-1157

AMGEN INC.,
Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,
Defendants-Appellants.

ON PETITION FOR PANEL REHEARING
AND REHEARING EN BANC

Before MICHEL, *Chief Judge*, NEWMAN, MAYER, LOURIE, *Circuit Judges*, CLEVENGER, *Senior Circuit Judge*,* RADER, SCHALL, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, *Circuit Judges*.

ORDER

A combined petition for panel rehearing and rehearing en banc was filed by the Appellee, and a response thereto was invited by the court and filed by the Appellants. The petition for rehearing was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response were referred to the circuit judges who are authorized to request a poll whether to rehear the appeal en banc. A poll

---

* Senior Judge Clevenger, who was on the original panel, participated only in decision on the petition for panel rehearing.

was requested, taken, and failed.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition for panel rehearing is denied.

(2) The petition for rehearing en banc is denied.

(3) The mandate of the court will issue on November 29, 2006.

MICHEL, *Chief Judge*, with whom RADER, Circuit Judge, joins, dissents in the denial of the petition for rehearing en banc in a separate opinion.

NEWMAN, *Circuit Judge*, dissents in the denial of the petition for rehearing en banc in a separate opinion.

LOURIE, *Circuit Judge*, concurs in the denial of the petition for rehearing en banc in a separate opinion.

RADER, *Circuit Judge*, dissents in the denial of the petition for rehearing en banc in a separate opinion.

GAJARSA, *Circuit Judge*, with whom LINN, and DYK, *Circuit Judges*, join, concur in the denial of the petition for rehearing en banc in a separate opinion.

MOORE, *Circuit Judge*, dissents in the denial of the petition for rehearing en banc in a separate opinion.

FOR THE COURT

Date

Jan Horbaly
Clerk

cc: Lloyd R. Day, Jr., Esq.
Carter G. Phillips, Esq.

November 22, 2006

MICHEL, *Chief Judge*, and RADER, *Circuit Judge*, dissenting from the denial of the petition for rehearing en banc.

Rehearing this case en banc would have enabled us to reconsider *Cybor*'s rule of de novo review for claim construction in light of our eight years of experience with its application. I have come to believe that reconsideration is appropriate and revision may be advisable.

In my view, four practical problems have emerged under the *Markman-Cybor* regime: (1) a steadily high reversal rate; (2) a lack of predictability about appellate outcomes, which may confound trial judges and discourage settlements; (3) loss of the comparative advantage often enjoyed by the district judges who heard or read all of the evidence and may have spent more time on the claim constructions than we ever could on appeal; and (4) inundation of our court with the minutia of construing numerous disputed claim terms (in multiple claims and patents) in nearly every patent case.

Our standard of review of no deference to the trial judge's claim constructions, expressed in *Cybor*, rests upon the premise that claim construction is always a purely legal exercise, devoid of factual content. We have likened claim construction to statutory construction. I believe that this analogy is open to serious question. In interpreting statutes, a judge, whether trial or appellate, essentially asks himself/herself, "What does the disputed term mean to me, the judge, as an artisan in the law?" With claim construction, on the other hand, the judge is supposed to inquire, essentially, "How would the average artisan in the relevant field of technology understand the disputed claim terms in the context of the rest of the patent, the prosecution history, and the prior art?"

It seems to me that the claim construction question often cannot be answered without assessing, at least implicitly,

what the average artisan knew and how she thought about the particular technology when the patent claims were written. To make such determinations, the trial judge necessarily relies upon prior art documents and other evidence concerning the skill of the ordinary artisan at the relevant time. Indeed, trial judges are arguably better equipped than appellate judges to make these factual determinations, especially in close cases. In such instances, perhaps we should routinely give at least some deference to the trial court, given its greater knowledge of the facts. Or, perhaps other adjustments to our current practice should be considered.

Whatever our resolution, however, I believe the time has come for us to re-examine *Cybor*'s no deference rule. I hope that we will do so at our next opportunity, and I expect we will.

NEWMAN, *Circuit Judge*, dissenting from denial of the petition for rehearing *en banc*.

The issue for rehearing *en banc* is the Federal Circuit's rejection of the district court's construction of the claim term "a therapeutically effective amount." My concern is with this court's methodology and rationale of claim construction, and with the sources on which the panel majority relied (or failed to rely) in arriving at its changed claim construction. The district court had correctly applied this court's precedent, requiring affirmance.

I

In brief, the panel majority construed the claims more broadly than the invention that was patented; thus the court ignored the patentee's purpose of writing claims that avoid the prior art — a purpose essential to every claim in every patent — by now construing the claims so that, as the panel majority recognized, they may read on the prior art. The patentee's purpose of including the critical limitation to "a therapeutically effective amount" of the genetically engineered erythropoietin (EPO) was to distinguish the prior art EPO isolates, which were not therapeutically effective to "heal or cure," in the district court's words. Thus this court's claim construction diverges from the specification and the prosecution history, and presents a claim construction that impinges on the prior art and thereby fosters invalidity. From this analytic method of claim construction and the denial of rehearing *en banc* I must, respectfully, dissent.

The methodology of claim construction that the court has here adopted raises issues that were laid to rest in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), where the *en banc* court disavowed the view that a patent claim can be construed more broadly than the invention to which it gives legal effect. In *Phillips* that unwarranted breadth was found in claim construction based on general dictionary definitions of

claim terms, rather than relying on the specific technical usage in the specification; in this case the unwarranted breadth is found in the court's claim construction that may embrace the prior art, despite the exclusion of that subject matter by the prosecution history.

The district court, construing the claims in light of the specification and the prosecution history, construed "a therapeutically effective amount" as "a quantity that produces a result that in and of itself helps to heal or cure." That construction was the basis on which the patentee distinguished its genetically engineered EPO from the chemically identical EPO in known isolates of naturally occurring EPO, for the prior art product contained insufficient EPO to heal or cure. Thus the claim limitation to "a therapeutically effective amount" of EPO was critical to allowance. During an extensive prosecution, the applicant stated that

> naturally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proven to be clinically effective, *and* is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low blood counts.

App. No. 113,178, *Amendment under Rule 16* at 4, June 5, 1989 (emphasis in original).

The record in the district court contains evidence, presented by persons experienced in this field of science, that the limitation to "a therapeutically effective amount" distinguishes the genetically engineered EPO from known EPO isolates. The district court construed the claims from the viewpoint of the skilled artisan, upon reading and understanding the specification and the restrictions flowing from the prosecution history. My concern about this court's

methodology is that the panel majority does not apply these standard tools of claim construction. The court's holding that "a therapeutically effective amount" includes any amount of EPO that exhibits a physiologic effect, whether or not the amount of EPO is adequate to provide therapy for any disorder, imparts to the claims the scope that was excluded during prosecution.

Although this court has urged caution in construing claims in order to preserve their validity, no precedent or logic requires that when more than one claim construction is available, the court must choose the broader one although it may invalidate the claim. *See Phillips*, 415 F.3d at 1327 (court may not construe claims as would be appropriate to preserve their validity unless "after applying all the available tools of claim construction . . . the claim is still ambiguous"); *see also Smith v. Snow*, 294 U.S. 1, 14 (1935) ("if the claim were fairly susceptible to two constructions, that should be adopted which will secure to the patentee his actual invention"); *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1556 (Fed. Cir. 1996) ("When claims are amenable to more than one construction, they should when reasonably possible be interpreted so as to preserve their validity.").

Here, the specification and prosecution history make clear that the claimed invention is the "therapeutically effective amount" of engineered recombinant EPO. As was explained to the patent examiner and again in the district court, the prior art isolates of EPO were ineffective to heal or cure. Just as the prosecution record cannot enlarge the claims beyond what the inventor has presented as his invention, so the court cannot enlarge the claims beyond the limitations imposed by the patentee. *See Phillips*, 415 F.3d at 1319 (rejecting definitions broader than the technical usage specific to the invention). The court in this case has departed from these fundamental principles. We should speak *en banc* to clarify that it is

appropriate, and necessary, to look at what has in fact been invented, prosecuted, and patented, and construe the claims accordingly.

II

I do not share the view, expressed here by some colleagues, that this court should not intrude upon panel decisions when major errors of claim construction are pointed out on petition for rehearing *en banc*. The Federal Circuit has a special obligation to provide predictability and consistency in patent adjudication, for our panel decisions are of nationwide effect; indeed, this obligation was a justification for the court's holding, a decade ago, that the district court's claim construction receives non-deferential review on appeal. This appellate position imposes on us the obligation to state the correct law, even on rehearing *en banc*. If the meaning of "therapeutically effective amount" is treated as a question of law, its correct definition as well as the methodology by which it is defined are squarely within the criteria for rehearing *en banc*. And if the meaning is recognized as a case-specific finding of fact, appellate review warrants deference to the trier of fact, a deference here lacking.

III

I continue to believe that findings of science/technology-based facts in patent cases should receive appellate review on the same basis as other science-based findings, guided by *Daubert* and the Court's ensuing elaborations. The Court's and our own precedent require the trial judge to evaluate scientific evidence and expertise from the viewpoint of a person experienced in the field of science, a framework that aptly fits evaluation of the technologic content and scope of patents, an analysis whose intermingling of fact and law is well served by the procedures and the adjudicatory skill of the district courts. The Federal Circuit's position that patent interpretation requires more rigorous appellate review than other fact/law issues has not well withstood the test of

experience. It is time to reopen the question and to rethink, *en banc*, the optimum approach to accuracy, consistency, and predictability in the resolution of patent disputes, with due attention to judicial structure, litigants' needs, and the national interest in invention and innovation.

LOURIE, *Circuit Judge* concurring.

I concur in the decision of the court not to rehear this case en banc. I do so, even though I agree that the panel erred in construing the claim limitation "a therapeutically effective amount." In my view, the panel dissent by Chief Judge Michel was correct, as was the decision by the district court and the current dissent by Judge Newman. However, I do not believe that every error by a panel is enbancable. A panel is entitled to err without the full court descending upon it.

Federal Rule of Appellate Procedure 35(a) provides that "[a]n en banc hearing or rehearing is not favored and ordinarily will not be ordered unless: (1) en banc consideration is necessary to secure or maintain uniformity of the court's decisions; or (2) the proceeding involves a question of exceptional importance." Our Internal Operating Procedures ("IOPs") state that "[a]mong the reasons for en banc actions are: (1) necessity of securing or maintaining uniformity of decision; (2) involvement of a question of exceptional importance; (3) necessity of overruling a prior holding of this or a predecessor court expressed in an opinion having precedential status; or (4) the initiation, continuation, or resolution of a conflict with another circuit." IOP 13(2).

This issue is thus enbancable only on the uniformity or exceptional importance grounds. However, the interpretation of "a therapeutically effective amount" with respect to this particular patent specification seems to me to be case-specific, and it does not therefore raise a question of uniformity of decision or exceptional importance. The term, while in my view incorrectly construed by the majority of the panel, does not necessarily apply to specifications of other patents. In addition, while the result may be of exceptional importance to the parties, it does not seem to be so to the law.

I therefore concur in the decision of the court not to rehear the case en banc, although I disagree with the majority's holding.

RADER, *Circuit Judge*, dissenting from denial of the petition for rehearing en banc.

I agree with the reasoning of Chief Judge Michel's and Judge Newman's dissents. Like them, I urge this court to accord deference to the factual components of the lower court's claim construction. Under current law, this court accords no deference whatsoever to a district court's claim construction. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1451, 1455-56 (Fed. Cir. 1998) ("[C]laim construction, as a purely legal issue, is subject to de novo review on appeal."). The Supreme Court recognized that, far from a "purely legal issue," claim construction "falls somewhere between a pristine legal standard and a simple historical fact." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996).

Quoting the Supreme Court, this court agreed with the Supreme Court's recognition that "the fact/law distinction at times has turned on a determination that, as a matter of sound administration of justice, one judicial actor is better positioned than another to decide the issue in question." *Cybor*, 138 F.3d at 1455. In this case, the district court's analysis of "therapeutically effective amount" deserved greater deference. As is often the case, the district court was better positioned than this court to reach the proper construction. After all the district court has more tools, more time, and more direct contact with factual evidence than this appellate body. *Id.* at 1477 (Rader, J., dissenting) ("Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, examining on site the operation of the principles of the claimed invention, and deliberating over the meaning of the claim language. If district judges are not satisfied with the proofs proffered by the parties, they are not bound to a prepared record but may compel additional presentations or

even employ their own court-appointed expert."). Indeed, in this case, the trial court held a nine-day trial, including testimony of artisans informed of the meaning of "therapeutically effective amount" at the time of invention. The trial court, while noting that it did not rely on expert testimony to construe the claim, specifically noted that such testimony offered during the trial fully supported the district court's claim construction. Given this court's rule toward limited reliance on extrinsic evidence in claim construction, *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1311 (Fed. Cir. 2001) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996)), district court judges have learned to disclaim any reliance on expert testimony. Yet, in this case the trial court took testimony for nine days – hardly necessary if the judge was merely reading and relying upon the intrinsic patent document alone.

The district court's construction of "therapeutically effective amount" also falls in line with prior opinions of this court and suggests that artisans in this field would accord the term its customary usage. *Geneva Pharm. v. GlaxoSmithKline*, 349 F.3d 1373, 1383 (Fed. Cir. 2003) (finding that "effective amount" is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite); *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 344 F.3d 1274, 1278 (Fed. Cir. 2003) (Because the patentee did not deviate from the accustomed meaning of the disputed claim term, the term "effective amount" is construed in view of its ordinary and customary meaning). Thus, I would grant en banc review.

GAJARSA, LINN and DYK, *Circuit Judges*, concurring in the denial of the petition for rehearing en banc.

We concur in the denial of rehearing en banc. Our concurrence should not be read as an endorsement of the panel's claim construction in this particular case, nor as an unqualified endorsement of the en banc decision in *Cybor Corp v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998). In an appropriate case we would be willing to reconsider limited aspects of the *Cybor* decision. In our view an appropriate case would be the atypical case in which the language of the claims, the written description, and the prosecution history on their face did not resolve the question of claim interpretation, and the district court found it necessary to resolve conflicting expert evidence to interpret particular claim terms in the field of the art. This is not such a case.

In this case the district court explicitly and repeatedly disavowed reliance on extrinsic expert evidence in construing the claim term "therapeutically effective." The district court noted that "[d]emonstrative exhibits were presented and references were made to certain expert testimony, but extrinsic evidence was not admitted." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 222 (D. Mass. 2004). Ultimately, the district court concluded:

> While the expert testimony does support the plain and ordinary meaning of the term since it defines what 'cure' means in the context of anemia patients, the Court will not rely on it to construe the claim, because even the *Altiris [Inc. v. Symantex Corp.*, 318 F.3d 1363 (Fed. Cir. 2003)] court made clear that it was looking to expert testimony merely to understand the technology—not to construe the term itself.

Amgen, 339 F. Supp. 2d at 230 n.27; *see id.* at 233 n.29 (noting that extrinsic evidence was not being used "to define the term").[1]

The district court proceeded to construe the claim "therapeutically effective" without resort to extrinsic expert evidence. It first "look[ed] to the plain and ordinary meaning of the words of the patent claim," *id.* at 229, then "review[ed] the specification to determine whether the patentee has used terms in a manner inconsistent with the ordinary meaning or has become his own lexicographer," *id.* at 232, and finally "consider[ed] the prosecution history to determine whether the applicant ha[d] made any express representations regarding the claim's scope," *id.* at 238. No deference is due a district court's legal interpretation of the claim language, written description, and prosecution history that an appellate court is equally competent to interpret.

Since the district court did not rest its interpretation on factual findings concerning conflicting expert evidence and neither the panel majority nor the dissent addressed this issue, we do not believe that this is the appropriate case in which to reconsider aspects of the *Cybor* decision.

---

[1] *See also id.* at 226 (noting that expert testimony "is extrinsic evidence to which resort ought to be had only 'if necessary'"); id. at 231 n.28 ("[T]he Court cannot rely on expert testimony to help construe the term 'therapeutically effective' unless absolutely necessary.")

MOORE, *Circuit Judge*, dissenting from the denial of the petition for rehearing en banc.

I dissent from this court's denial of the petition for rehearing en banc. First, let me begin by saying that under the court's present standard of de novo review, in my opinion the district court's construction of "a therapeutically effective amount" was correct. I need not articulate all the reasons that the claims, specification, prosecution history, and extrinsic evidence all support the interpretation given by the district court—the district court's own opinion and the panel dissent by Chief Judge Michel effectively do so. If the only issue were one of case-specific mistake, I would concur in the decision not to hear the case en banc. Federal Rule of Appellate Procedure 35(a) and our Internal Operating Procedures limit the use of en banc.

I dissent because I believe this court should have taken this case en banc to reconsider its position on deference to district court claim construction articulated in *Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1454-55 (Fed. Cir. 1998) (holding that claim construction was purely a matter of law and therefore subject to de novo review). Five judges of this court have written opinions in this case expressing disagreement with the two judge panel majority's claim construction even under the de novo standard of review.

In this case, the district court construed the term "a therapeutically effective amount" with the assistance of a technical advisor (an MIT Professor) and a Special Master. The district court opinion explains that the term was construed using the patent claims, the specification, the prosecution history, three different dictionaries, and prior art.[1]

---

[1] Dictionaries, technical treatises, and prior art disclosures are extrinsic evidence relied upon by the district court to construe this term. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp.2d 202, 226-228 (D. Mass. 2004) (detailing the dictionary definitions); *Id.* at 244 n.46 (explaining that the prior art disclosed to the patent examiner also

The opinion also explains that the claim construction is supported by the expert testimony presented by the parties in this case,[2] but then disavows using it to "define the term" or "construe the term" instead stating that it is being used to "understand the technology."[3]

I commend the district court for its thorough, detailed, thoughtful, and competent efforts in construing this claim limitation. The district court did everything we have asked it to do, and in my opinion, did it correctly. While this may not be a basis for taking the case en banc, reconsideration of the deference accorded to the district court in this case would have been. Therefore, I would grant en banc review.

---

supports the district court's interpretation). When the district court disavows use of extrinsic evidence, it seems to be focusing on expert testimony.

[2] *Id.* at 244-45 n.47 (finding that "two crucial witnesses for the defense conceded" points which support the district court's claim construction).

[3] The district court goes on to point out that the Federal Circuit precedent has created a "conundrum" by: "discouraging resort to extrinsic evidence while at the same time urging courts to begin claim construction by considering the plain and customary meaning of a term as understood by one skilled in the art." *Id.* at 226 n.23.

FILED
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SUPREME COURT, U.S.

(4)

No. 06-1291

IN THE

Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC.
(now known as AVENTIS PHARMACEUTICALS, INC.) AND
TRANSKARYOTIC THERAPIES, INC.
(now known as HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF IN OPPOSITION

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BRIEF IN OPPOSITION

The decision below raises neither of the questions petitioner asks this Court to review. In its effort to demonstrate otherwise, petitioner misstates the basis of the district court's ruling on claim construction, and mischaracterizes the panel's ruling on prosecution history estoppel.

Petitioner asks this Court to overturn the Federal Circuit's *de novo* standard of review and mandate appellate deference to the "factual determinations" that supposedly underlie district court claim constructions because, petitioner asserts, district courts have "superior access" to "extrinsic evidence," including expert testimony, that "crucially inform[s]" such rulings. Pet. at i, 19. But, the district court's claim construction in this case did not rest on any "findings of fact," and the district court repeatedly *disavowed* reliance on expert testimony. The court did so because the meaning of the phrase "therapeutically effective" does not turn on "technological mastery" or "key insights" into the treatment of anemia, *id.* at 14, 19. Rather, its meaning turns on a sentence in the specification where, as a matter of simple grammar, the patentee expressly equated the phrase with certain biological effects of erythropoietin ("EPO").

The panel did not mistakenly believe that these biological effects are "sufficient[] to treat anemia," as petitioner wrongly claims. *Id.* at 21. Instead, the panel found that the patentee had acted as is own lexicographer and, in a critical sentence of the specification, had given the phrase "therapeutically effective" a non-ordinary meaning. Thus, while petitioner fulminates about the reversal of a "careful and scientifically well-informed district court" claim construction, *id.* at 2, the centerpiece of that construction was the district court's grammatically nonsensical revision of the plain language of the specification. No deference is owed to a district court's demonstrably artificial reading of a patent specification.

Consideration of this issue is also entirely premature. Petitioner cites law review articles and judicial statements criticizing *Cybor Corp.* v. *FATS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc), and challenges its *de novo* standard of review as inconsistent with decisions of this Court and the Federal Rules of Civil Procedures. Pet. at 15 & nn.5 & 6, 18 & n.8, 21-23. But petitioner launched no such attack on *Cybor* below. Now, after several judges have stated a willingness to re-examine *Cybor*, Pet. App. 596a, 602a, 606a, petitioner claims that the decision "is here to stay," Pet. at 16, and asks this Court to overrule it based on arguments never raised below. This Court should address the question, if at all, only after the full airing of views that en banc consideration affords, just as this Court has done when addressing other principles of patent law.[1]

Nor does the panel's application of prosecution history estoppel in this case merit review. This fact-bound ruling was entirely faithful to the principles established by this Court in *Festo*, and erected no insurmountable barriers to rebuttal of the presumption of estoppel. Petitioner's hyperbolic claims to the contrary are demonstrably incorrect. Certiorari should be denied.

1a. The central premise of the first question petitioner seeks to raise is that the district court's construction of the phrase "therapeutically effective" rested on factual "findings." To create this impression, petitioner stresses that Judge Young received "tutorials from an M.I.T. scientist, listened to 32 days of testimony from 35 scientists, and read countless pages of written submissions." Pet. at 19, see also *id.* at 5, 7. From this, petitioner claims, the judge developed a

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[1] The following landmark cases followed en banc consideration by the Federal Circuit: *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17 (1997), and *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002).

"technological mastery" and "special familiarity" with the scientific field, *id.* at 14, that "crucially informed" his construction of the claim language. *Id.* at 19. "[D]rawing on all he had read, heard, and seen," *id.* at 14, petitioner claims that Judge Young made a "factual determination" that

> even though the specification associated certain biological changes with "therapy procedures" it would never occur to a *skilled practioner reading the specification* that (as the panel majority thought) an amount *merely* eliciting one of these changes would be a "therapeutically effective amount."

Id. at 21. Indeed, petitioner claims that Judge Young himself "repeatedly emphasized that his conclusions were informed by the expert testimony and his familiarity with the technology." *Id.* at 7-8.

Judge Young's decision flatly refutes this fanciful portrayal. In fact, he repeatedly emphasized that he was *not* relying on expert testimony or demonstrative exhibits to construe the claims. He explained that "[d]emonstrative exhibits were presented and references were made to expert testimony [during the *Markman* hearing], but extrinsic evidence was *not admitted*." Pet. App. 69a (emphasis added). This was because expert testimony "is extrinsic evidence to which resort ought to be had only *if necessary*." *Id.* at 76a (internal quotation marks omitted); see also *id.* at 81a n.25 (same); *id.* at 86a n.28 ("the Court cannot rely on expert testimony to help construe the term 'therapeutically effective' unless absolutely necessary"). And Judge Young made clear that it was not necessary to resort to such evidence. He stressed that, "[w]hile the expert testimony does support the plain and ordinary meaning of the term, . . . the Court *will not rely on it to construe the claim*." *Id.* at 85a n.27 (emphasis added). Instead, he used "extrinsic evidence . . . to understand the technology—*not to define the term*" "therapeutically effective." *Id.* at 89a n.29 (emphasis added). See also *id.* at 111a n.47 (noting that reliance on expert

testimony would have been "an alternate" interpretive route, which he had not employed). This is why, in its brief to the panel below, petitioner did not argue that Judge Young's claim construction was "crucially informed by . . . extrinsic evidence," Pet. at 19, and instead repeatedly stressed that he had properly and "carefully review[ed] the *intrinsic* record."[2]

Petitioner now quotes selectively and misleadingly from the opinion to try to show that, despite his statements and petitioner's own concession below, Judge Young did rely on expert testimony to construe the claims. Petitioner claims that the judge's claim construction "was based on [1] 'a careful review of the technology and its history' that [2] 'relied on extrinsic evidence,'" and that "his conclusions were informed by his [3] 'understanding of the technology.'" Pet. at 20. In the passage from which these three excerpts are lifted, however, Judge Young was not explaining his claim construction conclusions at all. He was rejecting *petitioner's argument* that, if "therapeutically effective" means the *in vivo* biological effects of EPO, two claims of a different patent would be redundant. Pet. App. 84a. In this very discussion, moreover, Judge Young emphasized, twice, that he was not relying on expert testimony "to construe the claim," but to understand the technology, *id.* at 84a-85a n.27, which illuminated the flaw in petitioner's redundancy argument.

More fundamentally, petitioner's misleading excerpts have nothing to do with the centerpiece of Judge Young's ruling—and the central flaw the panel majority identified in it. Because a patentee can serve as his or her own lexicographer and give terms non-ordinary meanings, Judge Young recognized that he had to make two determinations: "[w]hat is the plain and ordinary meaning of 'therapeutically effective,' and does the intrinsic evidence define the term differently than its plain and ordinary meaning?" Pet. App. 76a n.22.

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[2] Br. of Plaintiff-Appellee, Amgen Inc. at 12, No. 05-1157 (Fed. Cir. filed May 17, 2005) (emphasis added); *see also id.* at 16, 19, 28.

Petitioner tried to rely on expert testimony before Judge Young to show what the plain meaning of the term was. See *id.* at 72a, 76a. But the critical error the panel identified in Judge Young's claim construction concerned the second determination—his conclusion that the patentee did not give the phrase "therapeutically effective" a non-ordinary meaning in the specification. In so ruling, Judge Young made no "factual determination" about how skilled practioners would read the specification, cf. Pet. at 21. Instead, his conclusion rests on a grammatically nonsensical reading of a critical sentence in the specification.

That sentence provides that:

> "to the extent that the polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin *therapy procedures* practiced on mammals, including humans, *to develop any or all of the effects* herefore attributed in vivo to EPO, e.g., [1] stimulation of reticulocyte response, [2] development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), [3] erythrocyte mass changes, [4] stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, [5] as indicated in Example 10, increasing hematocrit level in mammals."

Pet. App. 88a (emphases added and deleted).

The panel in the first appeal observed that this language appears to teach that all five of the listed responses are encompassed by the term "therapeutically effective," *id.* at 400a-01a, even though only a sustained increase in hematocrit actually cures disease. On remand, Judge Young conceded that "use of the words 'therapy procedures' supports the interpretation that a 'therapeutically effective amount' encompasses an amount that would result in the biological effects" listed, whether or not they heal or cure. *Id.* at 90a; see also *id.* at 89a (the specification "suggests" that "the

biological effects[] are a type of effective therapy"). But Judge Young rejected this clear meaning. He read the specification, in the following artificial manner, to describe the claimed EPO as "'conspicuously suitable for'":

> (a) "use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, . . ." *and*,
>
> (b) "as indicated in Example 10, increasing hematocrit level in mammals."

Id. at 89a (ellipses in original). So viewed, he believed, the specification explains that the claimed EPO elicits "'any or all' of the effects that natural EPO does—*and more*." *Id.* at 90a (emphasis added).

As a matter of basic grammar, this reading is utterly untenable. The sentence identifies "any or all" of the five biological effects as "effects' of "therapy procedures." The patentee easily could have said that the claimed composition is suitable for use in therapy because, in addition to eliciting all of the non-curative biological effects of natural EPO, it elicits something more—a sustained increase in hematocrit levels. But the sentence manifestly does not say this. Nor does it "make[] clear that 'any or all' only modifies those effects previously attributed to natural EPO." *Id.* The phrase "any or all" plainly modifies all five of the listed effects. Judge Young's "reading" of this key sentence is not an interpretation of it at all; his "reading" re-writes the sentence.

Moreover, Judge Young's attempt to bifurcate, and thereby re-write, the sentence produces a clear grammatical error. As noted above, the specification lists five effects previously attributed *in vivo* to EPO: "[1] stimulation of reticulocyte response, [2] development of ferrokinetic effects . . . [3] erythrocyte mass changes, [4] stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, [5] as indicated in Example 10, increasing hematocrit level in mammals." *Id.* at

88a (emphasis omitted). If the patentee intended to create two distinct categories, there should be an "and" before the fourth effect, which, under Judge Young's "reading," is the last of the effects listed in the first category. As this Court has explained when addressing a similar attempt to re-write (through "interpretation") a similarly structured sentence, courts should eschew interpretations of binding legal instruments that produce such ungrammatical omissions. See *Arcadia, Ohio* v. *Ohio Power Co.*, 498 U.S. 73, 79 (1990) (rejecting interpretation of statute for this reason).

Just as important, the sentence, even when bifurcated, still does not exclude the listed biological effects of natural EPO from the roster of therapeutic effects. The first part of the bifurcated sentence still states that petitioner's product is "'conspicuously suitable for use in erythropoietin *therapy procedures* . . . to develop any or all of the effects'" listed in Judge Young's first category. Pet. App. 88a. By referring to the biological effects of natural EPO as effects of "therapy procedures," the specification inescapably deems these effects therapeutic, as Judge Young acknowledged. *Id.* at 90a.

No deference is owed to this tortured and ungrammatical reading of the specification, which, as the panel majority correctly explained, rests on an "artificial distinction between the first four effects listed . . . and the fifth effect." *Id.* at 14a. Judge Young plainly did not rest that reading on any "factual finding" about how "skilled practitioners" would read the sentence. In fact, he never refers to "skilled pracitioners" or a "person of ordinary skill in the art" anywhere in his lengthy discussion of the specification. See *id.* at 87a-97a.[3] And,

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[3] In analyzing the specification, Judge Young referred briefly to extrinsic evidence, again "not to define the term," Pet. App. 89a n.29, but to support his statement that the natural reading of this key sentence led to a mistake: increased hematocrit levels, he stated, were not previously attributable to natural EPO. *See id.* at 89a-90a. This "mistake" is debatable: natural EPO isolates did increase hematocrit, but did not lead to *sustained* increases, something the specification does not identify as a

while petitioner baldly asserts that it "would never occur to a *skilled practioner reading the specification* that . . . an amount *merely* eliciting one of these changes would be a 'therapeutically effective amount,'" such a reading is compelled by simple rules of grammar, which are no less familiar to hematologists than they are to federal judges.

Nor is it true that the panel majority failed to appreciate a scientific principle that Judge Young gleaned from tutorials and expert testimony—*i.e.*, that the first four effects listed in the specification's key sentence are "early indicators of red blood cell generation [that] are necessary, but not sufficient, to treat anemia." Pet. at 21. The panel majority below nowhere suggested that it thought these "early indicators" were healing or curative. To the contrary, it concluded that the patentee had deemed certain biological effects "therapeutic" even though "[t]hose effects do not *necessarily* include curing disease." Pet. App. 15a.

In short, this case provides no opportunity for the Court to address the first question the petition purports to present. The district court's claim construction does not rest on factual determinations "crucially informed" by expert testimony or other extrinsic evidence to which district courts have superior access. It rests on a manifestly ungrammatical and untenable re-writing of a key sentence in the specification. The legal issue petitioner urges this Court to address, therefore, can have no effect on the judgment in this case. Even under the "clearly erroneous" standard of review petitioner advocates,

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previous effect. But even if the specification did erroneously identify an increase in hematocrit as an effect of natural EPO isolates, that would not justify Judge Young's re-writing of the sentence. First, another mistake lies at the very "heart of [petitioner's] invention," *id.* at 242a, *i.e.*, that mature EPO has a 166-amino acid sequence. Second, and more fundamentally, if it is factually inaccurate to state that increasing hematocrit was an effect previously attributed to EPO isolates, that inaccuracy is not avoided by Judge Young's re-writing of the sentence, which, even as he bifurcates it, still describes "increasing hematocrit" as an effect previously attributed to EPO isolates.

no deference would be owed the district court's tortured "reading" of the specification.

b. Not only is this issue not presented, but consideration of the issue is entirely premature. Petitioner launches a broad-based attack on the *Cybor* decision, citing criticisms of it by law reviews and members of the Federal Circuit, and claiming that its *de novo* standard of review conflicts with Rule 52 of the Federal Rules of Civil Procedure as well as with this Court's decisions in *Markman*, *Dennison Manufacturing Co.* v. *Panduit Corp.*, 475 U.S. 809 (1986) and *Graham* v. *John Deere Co. of Kansas City*, 383 U.S. 1 (1996). Pet. at 15 & nn.5 & 6, 18 & n.8, 21-23. But petitioner launched no such attack on *Cybor* below, and this Court should not be the first to entertain these arguments.

As noted, before the panel, petitioner did not advocate deference to a fact-based claim construction. Rather, it argued that Judge Young had properly construed the claim based on his review of the intrinsic record. Nor did petitioner challenge *Cybor* in its petition for rehearing en banc. It simply noted that *Markman* did not establish a standard of review and argued that *Cybor* itself required "[s]ome measure of appellate respect" for district court claim constructions.[4] Petitioner did not mention any of the law review articles it cites now. It did not cite or mention Rule 52 or the decisions in *Dennison* or *Graham*. And it identified no conflict between *Cybor* and *Markman*.

Despite these failures, several members of the Federal Circuit expressed a willingness to re-examine *Cybor*. Pet. App. 596a, 602a, 606a. Those expressions flatly belie petitioner's claim that *Cybor* "is here to stay." Pet. at 16. In light of that willingness, moreover, this Court should not entertain review of an important precedent based on

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[4] Plaintiff-Appellee, Amgen Inc.'s Combined Petition for Panel Rehearing and Rehearing *En Banc* at 12-13, No. 05-1157 (Fed. Cir. filed Aug. 17, 2006).

arguments never raised below. Instead, it should address the issue, if at all, only with the benefit of the full airing of views that en banc consideration affords.

This is particularly true given the facile nature of many of petitioner's attacks on *Cybor*. Petitioner claims, for example, that the "factual findings" underlying claim constructions are indistinguishable from those that underlie obviousness determinations, and should be subjected to the same clearly erroneous standard of review. Pet. at 18, 21. But this case underscores the questionable nature of this analogy. Federal judges have no independent ability to determine the scope and content of prior art, the differences between prior art and a claimed invention, the level of ordinary skill in the pertinent art, or what the prior art would "teach" to a person of such skill. See *Graham*, 383 U.S. at 17. But federal judges are fully competent to apply the rules of grammar, and there is no reason to suppose that persons of skill in a particular scientific field employ different grammatical rules, or would simply ignore such rules.

Indeed, in *Markman* itself, this Court recognized that the credibility of experts would typically be "subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole." 517 U.S. at 389. In this case, for example, if an expert had claimed that no skilled practitioner would read the specification's key sentence to deem non-curative effects therapeutic, that testimony would not have been credible for the same reasons Judge Young's "reading" is incorrect. A "factual finding" based on such testimony should not be entitled to deferential review. Petitioner's suggestion, therefore, that there is no meaningful difference between claim constructions and obviousness determinations is mistaken.

Thus, while petitioner seeks to portray *Cybor*'s *de novo* standard of review as a failed experiment that has been

"lambasted for years by bench, bar and academy," Pet. at 2, there are strong reasons to doubt this critique and, as this case demonstrates, equally strong reasons to doubt the wisdom of the highly deferential standard of review petitioner advocates. Even in a case that squarely presented the question petitioner seeks to raise, these reasons would militate against review in the absence of en banc consideration. Here, where the question is not even presented, they simply underscore why review should be denied.

2. The panel's straightforward and fact-bound application of the prosecution history estoppel principles this Court established in *Festo* likewise raises no issues worthy of review. Indeed, there was no dissent from this part of the panel decision, and petitioner did not even mention it in its petition for rehearing and rehearing en banc. In seeking review of that ruling now, petitioner repeatedly mischaracterizes the decision below.

Petitioner claims that the panel's decision announces a "near abolition of the doctrine of equivalents in any case in which a patent has been amended," by converting *Festo*'s second basis for rebutting the presumption of estoppel into a "circular and insurmountable" barrier, and "destroy[ing] the residual *Festo* criterion." Pet. at 26, 28 (capitalization altered; internal quotation marks omitted). Even the most cursory reading of the panel decision refutes these hyperbolic claims. Far from announcing any sweeping standards, the panel undertook a careful and detailed examination of the file wrapper, petitioner's extrinsic evidence, the district court's reasoning and petitioner's arguments on appeal. Pet. App. 25a-40a. In finding that *Festo*'s exceptions did not apply, the panel announed no new rules or principles, nor any hostility towards the doctrine of equivalents.

Petitioner contended that it added a reference to "Figure 6" (which reflects an EPO with 166 amino acids) in order to limit the claims of its '080 patent to human EPO and thereby avoid a double-patenting rejection in light of another of its

patent ("the '933 patent"). The panel properly rejected this argument for two reasons. First, it explained that, in an interim amendment, petitioner had limited these claims to EPO with the 166 amino acids of Figure 6 "'or a fragment thereof.'" Pet. App. 37a. This amendment literally embraced defendants' 165-amino acid product, but did not avoid double-patenting, because "an incomplete amino sequence of Figure 6 (a 'fragment') was encompassed by both [petitioner's] application and the '933 patent." *Id.* Petitioner therefore deleted the phrase "or fragment thereof" to overcome the double-patenting problem. The panel correctly held that, where an amendment surrendering sequences of less than 166 amino acids was "central to the allowance" of the claims-in-suit, a claimed equivalent of 165 amino acids was not merely "tangential" to the purpose of the amendment. *Id.* at 37a-38a.

Petitioner is simply wrong in asserting that its need to avoid duplication has no significant relationship to the distinction between 165 and 166 amino acids. Petitioner chose to seek two distinct legal monopolies, the '933 and '080 patents; to do so, it agreed to limit the claims of the latter to products with 166-amino acids. Petitioner sued respondents under its other monopoly, the '933 patent, but the claims of the '933 patent asserted against respondents have been declared invalid. Petitioner now seeks to disavow the limits to which it agreed in order to obtain its second patent, the '080, and to reclaim, through the doctrine of equivalents, what it purposely surrendered in order to get two patents. This is a paradigmatic situation for use of prosecution history estoppel, and its application on these facts erects no "insurmountable" barrier to use of the doctrine of equivalents in future cases.

Second, the panel properly rejected petitioner's assertion concerning the "pupose" of the amendment. Petitioner argued that it sought to limit the claims of the '080 patent to "human" EPO. But it is undisputed that, when it added the reference to Figure 6, petitioner knew that mature human

EPO did not have 166-amino acids. Moreover, in interim amendments, petitioner added the word "human" when referring to EPO, but then deleted that language from the claims. In light of these facts, the panel correctly ruled that the purpose of an amendment specifying 166 amino acids was not to limit the claims to "human" EPO. *Id.* at 38a. This ruling, which is inherently fact-bound, "erect[s] [no] roadblock across the most important avenue for avoiding estoppel." Pet. at 28.

Finally, while petitioner accuses the panel of destroying *Festo*'s residual, "some other reason" exception, it is petitioner that proposes a radical, and improper, new role for this exception. Even though petitioner *knew* when it amended its claims that mature human EPO has 165, not 166, amino acids, petitioner claimed that it could not have reasonably been expected to claim a 165-amino-acid sequence because those skilled in the art would have interpreted the reference to the 166 sequence of Figure 6 to encompass a 165-amino acid equivalent. As the panel recognized, this turns the concept of estoppel on its head.

The relevant inquiry is not whether skilled practitioners reading claims to a polypeptide with 166 amino acids would assume it covered polypeptides with 165 amino acids. The question is whether such a person who reviewed the file wrapper and saw that petitioner deleted references to "human" EPO and "fragments" of a 166-amino acid sequence would think that the patentee nevertheless intended to claim a mature human EPO sequence of 165 amino acids. The answer to that question is obviously no unless the patentee comes forward with "some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." *Festo*, 535 U.S. at 741. If a patentee can simply assert that he did not think he needed to bother to claim a known substitute because it was an obvious equivalent, then the principle of prosecution history estoppel is rendered meaningless. Because Amgen

knew of the equivalent, "could have simply claimed mature human EPO," but "still chose to claim the incorrect 166-amino acid sequence," it had failed to meet *Festo*'s third exception. Pet. App. 39a-40a. That ruling is plainly correct, and raises no issues warranting this Court's attention.

CONCLUSION

For all of the foregoing reasons, the petition should be denied.

Respectfully submitted,

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No. 06-1291

In the Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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REPLY BRIEF FOR PETITIONER

The petition for a writ of certiorari presented two broad, recurring legal issues of profound importance to patent litigation and the judicial process. One of them – *de novo* review of claim construction – cries out for this Court's attention, as three Federal Circuit en banc decisions, mountains of scholarly and judicial criticism, and numerous amicus briefs in past cases attest.[1] The other issue has *already* twice come to this Court, yet the Federal Circuit continues to defy this Court's rulings.

Respondents' brief in opposition proceeds as if petitioner had raised only fact-bound, case-specific issues. By arguing at length the merit of their construction of the term "therapeutically effective,"[2] respondents hope to distract the Court from the issue raised by this petition, which is whether the Federal Circuit should defer to the fact-based determinations of district courts regarding patent claim construction. Respondents duck that issue by resting on the same flawed premise as did the panel majority, namely that claim construction is an arid textual or grammatical exercise that appellate judges are as competent as district judges to perform. But patent claims must be interpreted from the standpoint of a skilled practitioner of the relevant art (in this case, a competent physician) – something that a district court, not an appellate court, is far better equipped to determine. Respondents refuse to engage this point, implicitly *assume* that their paradigm is correct, and then attempt to show that, under their paradigm, they win. Those diversionary tactics should not succeed.

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[1] Amicus briefs are anticipated in the present case as well. They are due – and respondents' brief in opposition was due – April 25, 2007. Only because respondents filed their brief in opposition 19 days before the due date is this case being distributed before the amicus briefs are filed.

[2] Though respondents try to obscure this fact, their construction of "therapeutically effective" notably rests entirely on their parsing of one sentence of the specification that *did not even use* the phrase "therapeutically effective." See p. 7, *infra*.

1.a. This case produced six opinions dissenting from or concurring in the denial of rehearing en banc. Five of those opinions addressed whether the Federal Circuit should change its entrenched practice of reviewing *de novo* all aspects of claim construction. Pet. App. 596a-602a, 604a-609a. Yet respondents argue that that issue is not even *presented* in this case. They are wrong.

Respondents' main argument is that their claim construction is so clearly correct – and Judge Young's so clearly wrong – that they would have prevailed under any standard of review. But respondents' interpretation is not correct. See pp. 6-9, *infra*. The fact that at least five members of the Federal Circuit agreed with Judge Young's claim construction (Pet. App. 43a, 598a, 603a, 604a, 608a) belies respondents' contention that their construction is so transparently right that the standard of review could have made no difference. A deferential standard would have required the Federal Circuit to accept the district court's factual determinations on two critical issues: (i) how the state of the art informed a proper understanding of the specification, and (ii) the knowledge of a person skilled in the art of the differences between mere biological effects and a therapeutically effective result.

b. Respondents also argue (Br. in Opp. ("BIO") 9) that petitioner did not preserve its challenge to plenary *de novo* review of claim constructions. That assertion is utterly mystifying. The three-judge panel was bound by prior en banc decisions to apply *de novo* review, so petitioner had no reason to make a futile request that the panel itself do otherwise. Petitioner certainly argued that the district court's claim construction was correct and should have been affirmed. Petitioner's first opportunity to challenge the standard of review was after the panel used *de novo* review to adopt its own misguided claim construction.

The rehearing petition's first sentence was: "Once again, a divided panel of this Court has swept aside a meticulous and well-reasoned district court claim construction in favor of its

own de novo construction." Argument heading II.C of the rehearing petition was "The Majority Decision Transgresses the Boundaries of Appellate Review." That section explained that, even when an ultimate conclusion is reviewed *de novo*, "the Supreme Court has made clear that 'a reviewing court should take care * * * to review findings of historical fact only for clear error.'" After presenting a range of arguments for deferential review of the factual determinations undergirding a claim construction, the petition concluded (at 15):

> If allowed to stand, the majority's decision to substitute its de novo construction for that of the district court will send a powerful yet debilitating message to district courts and litigants alike: there is little or no point to careful and considered efforts to construe the meaning of disputed claim terms to those skilled in the art because the Federal Circuit will substitute its own claim construction irrespective of their efforts. * * * The Court should hear this issue en banc because the panel's decision is inconsistent with both Federal Circuit and Supreme Court precedent.

It is irrelevant that "[p]etitioner did not mention [most] of the law review articles it now cites," or some of the other authorities the certiorari petition cites. BIO 9. "Although the Court generally declines to review *issues* not pressed or passed upon in the lower courts, it has allowed petitioners to make new *arguments* in support of claims properly presented below. * * * [T]he ability to introduce such 'new arguments' [i]s a 'traditional rule' * * *." STERN ET AL., SUPREME COURT PRACTICE § 6.26, at 421 (8th ed. 2002) (quoting *Lebron* v. *Nat'l R.R. Passenger Corp.*, 513 U.S. 374, 379 (1995)).

The Federal Circuit's judges understood that the rehearing petition called *Cybor* into question. *E.g.*, Pet. App. 596a (Michel, C.J., dissenting from denial of rehearing en banc) ("Rehearing this case en banc would have enabled us to reconsider *Cybor*'s rule of de novo review for claim construction in light of our eight years of experience with its application."). The issue is properly before this Court.

c. Also surprising is respondents' assertion that review is "entirely premature," BIO 9, because review of Federal Circuit decisions should await "the full airing of views that en banc consideration affords," BIO 2, 10. For one thing, none of the five patent cases in which this Court heard argument last Term and this Term was resolved en banc.[3] In any event, the views of Federal Circuit judges (and amici) on the propriety of *de novo* review of claim construction *have* been aired en banc – three times, not even including the separate opinions in this very case. *Markman* v. *Westview Instruments, Inc.*, 52 F.3d 967, 981 (Fed. Cir. 1995) (en banc), aff'd on other grounds, 517 U.S. 370 (1996); *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc); *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1328 (Fed. Cir. 2005) (en banc), cert. denied, 126 S. Ct. 1332 (2006). The numerous majority, concurring, and dissenting opinions in all of these cases more than join issue on the merits of *de novo* review.

What is more, the consistent battle lines in these cases show that the en banc Federal Circuit is not going to revisit this subject. Respondents say that the willingness expressed by "several members" of the Federal Circuit to reexamine *Cybor* "flatly belie[s] petitioner's claim that *Cybor* is here to stay." BIO 9. In the twelve years since *Markman*, however, the dissenting faction's "several members" have never come close to assembling a majority. If respondents are trying to imply that three judges' "willing[ness] to reconsider limited aspects of the *Cybor* decision" in an "atypical case" (Pet. App. 606a) creates

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[3] See *AT&T Corp.* v. *Microsoft Corp.*, 414 F.3d 1366 (Fed. Cir. 2005), cert. granted, 127 S. Ct. 467 (2006); *Teleflex, Inc.* v. *KSR Int'l Co.*, 119 Fed. Appx. 282 (Fed. Cir. 2005), cert. granted, 126 S. Ct. 2965 (2006); *MedImmune, Inc.* v. *Genentech, Inc.*, 427 F.3d 958 (Fed. Cir. 2005), rev'd, 127 S. Ct. 764 (2007); *MercExchange, L.L.C.* v. *eBay, Inc.*, 401 F.3d 1323 (Fed. Cir. 2005), vacated, 126 S. Ct. 1837 (2006); *Metabolite Labs., Inc.* v. *Lab. Corp. of Am. Holdings*, 370 F.3d 1354 (Fed. Cir. 2004), cert. granted, 126 S. Ct. 543 and 126 S. Ct. 601 (2005), cert. dismissed, 126 S. Ct. 2921 (2006).

a possibility that at some future time the en banc Federal Circuit finally will fix its mistake, that prediction is groundless. As the petition explained (at 19), even if the views of Judge Gajarsa were to prevail en banc, the Federal Circuit's *de novo* standard of review *still* would be in place (except in the rare case in which a district court expressly rested a definition on disputed expert testimony), and *still* would be wrong.[4]

d. In yet another effort to pretend that this case does not even *present* the issue of *de novo* review of claim construction, respondents (echoing Judge Gajarsa's concurrence) conflate *reliance on extrinsic evidence* with *resolving issues of fact*. The fact that Judge Young "properly and 'carefully review[ed] the *intrinsic* record'" (BIO 4 & n.2, quoting and adding emphasis to Amgen C.A. Br. 12) in no way makes his determinations any less factual. Rather, this Court has *already* held in the context of obviousness determinations that ascertaining "the scope and content of the prior art," "differences between the prior art and the claim at issue," and "the level of ordinary skill in the pertinent art" are *factual* determinations – inherently, and not just when those determinations are made based on extrinsic evidence. *Graham* v. *John Deere Co.*, 383 U.S. 1, 17 (1966). Those determinations are no less factual when they underlie a claim construction such as Judge Young's in this case. See Pet. 18-21. Thus, it would not matter even if were true that Judge Young "was *not* relying on expert testimony or demonstrative exhibits," BIO 3.

In any event, respondents protest too much. Judge Young did in fact draw heavily on the extrinsic testimony – and repeatedly acknowledged that fact. See Pet. 7-8, 19-21. That he did so

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[4] Among other problems (see Pet. 19, 22), Judge Gajarsa's view treats the specification and prosecution history – merely because they are considered intrinsic rather than extrinsic evidence and are documentary in nature – as items to be interpreted *de novo* on appeal. But Federal Rule of Civil Procedure 52(a) and *Anderson* v. *Bessemer City*, 470 U.S. 564 (1985), require appellate deference to factual findings based on documentary evidence.

under the rubric of "understand[ing] the technology" rather than "defin[ing] the claim term" is simply a function of the rules of the claim construction road. Judge Young was trying to avoid the pitfall of merely accepting a particular expert's say-so as to the definition of a claim term. But claim construction is necessarily informed by technical understanding. In trying to discern how one of skill in the art would understand the claim in the context of the specification, the judge properly drew on extrinsic evidence. See also Pet. 18 & n.8.

e. Respondents' brief in opposition ultimately rests on the same fallacy that led the panel majority astray. That fallacy – sometimes called "hypertextualism," see Craig Allen Nard, *A Theory of Claim Interpretation*, *in* FOUNDATIONS OF INTELLECTUAL PROPERTY LAW 122, 124-125 (Robert P. Merges & Jane C. Ginsburg, eds. 2004) – is that claim construction is a mere textual or grammatical exercise that appellate judges are just as competent as district judges to perform. But see Pet. 22-24.

Respondent, for example, relies on *Arcadia, Ohio* v. *Ohio Power Co.*, 498 U.S. 73 (1990), as support for the proposition that courts should attend to the rules of grammar in construing legal instruments. BIO 7. But in that case the Court was interpreting an Act of Congress, not a document reflecting specialized technical understanding. And even in *Arcadia* a grammatical difficulty with a particular reading of a statute was just the starting point of analysis. The longer portion of the Court's opinion rejecting that interpretation tried to make overall sense of the statutory provision at issue. 498 U.S. at 80-85.

In construing a patent, a court may of course start with rules of grammar, but its task is otherwise different from statutory interpretation. As Chief Judge Michel explained below:

> In interpreting statutes, a judge, whether trial or appellate, essentially asks himself/herself, "What does the disputed term mean to me, the judge, as an artisan in the law?" With claim construction, on the other hand, the judge is supposed to inquire, essentially, "How would the average artisan in the relevant field of technology understand the

> disputed claim terms in the context of the rest of the patent, the prosecution history, and the prior art?"

Pet. App. 596a. "What seems clear to a judge may read otherwise to a skilled designer." *In re Mahurkar Double Lumen Hemodialysis Catheter Patent Litig.*, 831 F. Supp. 1354, 1359 (N.D. Ill. 1993) (Easterbrook, J., sitting by designation).

Here, an artisan in the relevant field simply would not understand "therapeutically effective amount" to mean an amount that does *not* heal but merely produces biological effects listed in the specification. To begin with, although respondents claim that "the patentee had acted as its own lexicographer and, in a critical sentence of the specification, had given the phase 'therapeutically effective' a non-ordinary meaning," BIO 1, ***the single sentence of the specification that constitutes respondents' entire case does not use the term "therapeutically effective."*** See Pet. App. 92a. It is a strange act of "lexicograph[y]" that defines one term by using a *different* term in a supposedly non-ordinary way.

The sentence on which respondents rely is set forth – without the bracketed numbers misleadingly inserted by the brief in opposition (at 5) – in the margin.[5] The passage discusses *why and how* the invention is "suitable for use" in "therapy procedures." It does not redefine – or even *use* – the term "therapeutically effective," the word "amount," or the phrase "therapeutically effective amount." There is no effort to redefine the critical phrase used in Claim 1 of the '422 patent.

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[5] "Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects * * *, erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals." Pet. App. 88a.

Respondents misrepresent the opinion below when they say that "the centerpiece" of Judge Young's claim construction was a misreading of a single sentence in the specification. BIO 1, 4. The centerpiece, if there was one, was the undisputed plain and customary meaning of the term "therapeutically effective," which Judge Young – in effect standing in the shoes of a competent physician reading the patent – determined was not altered by anything in the patent or its prosecution history, properly understood. Pet. App. 75a-109a. Respondents acknowledge that the phrase must be given a "non-ordinary meaning" (BIO 1) for them to prevail, even as they point to a sentence that does not use the phrase as their only support for departing from its ordinary meaning.

Without the technical understanding that Judge Young gained, the specification's association of "therapy procedures" with a set of biological effects might suggest that the effects themselves are a type of therapy. BIO 5-6. But, as Judge Young found, that reading rested on "a *factually* incorrect" proposition. Pet. App. 90a (emphasis added).[6] Amgen's reading, by contrast, "comport[ed] with the Court's understanding – developed over the course of two intensive trials – of what hematocrit actually measures" (*id.* at 91a). Moreover, the court came to understand what the skilled worker knew – that the biological responses listed in the specification were precursors to a therapeutic effect, but in and of themselves provided no benefit to a patient. These are the very factual findings to which the Federal Circuit should have deferred.

Respondents' mantra is that Judge Young's reading of the sentence was "ungrammatical," BIO 1, 5, 6, 7, 8, but not even the panel majority went that far, and for good reason. Omitting "and" before the last item in a list following "e.g." is familiar

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[6] Respondents describe Judge Young's factual finding as "debatable." BIO 7 n.3. Choosing one of two "debatable" versions of facts, however, is exactly the function of trial proceedings, so respondents' assertion only helps prove petitioner's point. Respondents do not suggest that the finding was clearly erroneous. See Fed. R. Civ. P. 52(a).

shorthand, and hardly renders a reading so "tortured," *id.* at 7, that the need to avoid it trumps the understanding in the technical field.[7] Even if "simple rules of grammar" are "no less familiar to hematologists than * * * to federal judges," *id.* at 8, there was unrebutted testimony from a physician who agreed with Amgen's reading of the specification. 11/3/03 Tr. 658-659 (The sentence at issue "go[es] from the in vitro effects to the in vivo biologic effects and then increasing hematocrit levels, *both the biologic and eventually a therapeutic effect.* * * * So I think it shows an evolution of the use of erythropoietin, from in the laboratory to biological effects to, *finally to potential therapy.*") (emphasis added).

2. Respondents' approach to the doctrine-of-equivalents issue is equally mistaken. As an initial matter, respondents conceded below and do not here dispute that, contrary to the court of appeals' practice, the factual findings underlying a determination under *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), should be reviewed deferentially. See Pet. 11, 29-30. Nor do respondents contest that, if the panel *had* displayed appropriate deference, it would have affirmed. What respondents call a "fact-bound application," BIO 11, is really an aggressive foray into matters best left to the district court, subject to review for clear error.

Even on the merits, however, respondents are mistaken. Respondents argue that, because petitioner deleted an interim amendment claiming EPO with reference to the sequence of Figure 6 "or a fragment thereof," petitioner has surrendered its claim to *any* EPO with fewer than 166 amino acids. BIO 12. But that is exactly the kind of rigid approach to estoppel that has become the Federal Circuit's hallmark and that this Court

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[7] Moreover, without Judge Young's "bifurcation," the sentence has a much larger textual problem. As Judge Young pointed out, Pet. App. 90a, the phrase "in mammals" in the last item of the series would be redundant with "practiced on mammals" earlier in the sentence.

rejected in *Festo* and *Warner-Jenkinson* v. *Hilton Davis Chem. Co.*, 520 U.S. 17 (1997). Pet. 27, 28.

Even though Judge Young construed the claim as not literally including the 165-amino-acid sequence, he recognized the triviality of the distinction between 165 and 166 amino acids. (In fact, Amgen's own product is a 165-amino-acid polypeptide.) And he recognized, too, that the reasons for the amendments at issue – to avoid redundancy with another patent – had *nothing to do with* the distinction between 165 and 166 amino acids. Respondents' contentions to the contrary, like the panel's, make the tangentiality rebuttal criterion unattainable because respondents focus, circularly, only on the *result* of the amendment – which logically *must* be related to the distinction at issue – rather than on the *reason* for the amendment, which may in fact bear only a tangential relation to the distinction between the literal terms of the claim and the equivalent.

Respondents' treatment of the "some other reason" exception is similarly flawed. Respondents first misleadingly suggest that petitioner focused only on how a skilled practitioner would read the claims, not the prosecution history. BIO 13. But, as petitioner explained, Judge Young determined that one of skill in the art would not understand the amendments in the prosecution history as surrendering a claim to EPO with 165 amino acids. See Pet. 9, 28. Moreover, in asking only whether petitioner *could have* claimed EPO with 165 amino acids, BIO 13-14, respondents (like the panel) read the reasonableness element out of this criterion and collapse it into the foreseeability test, which has never succeeded on appeal. Pet. 29. It is thus respondents, not petitioner, who render this Court's precedents "meaningless," BIO 13.

CONCLUSION

For the foregoing reasons and those stated in the petition, the petition for a writ of certiorari should be granted.

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AMGEN, INC.,
Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),
Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals For the Federal Circuit

BRIEF OF THE AMERICAN BAR ASSOCIATION AS *AMICUS CURIAE* SUPPORTING PETITIONER

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INTEREST OF THE AMICUS CURIAE[1]

The American Bar Association ("ABA"), with more than 413,000 members, is the leading national organization of the legal profession. Its members come from each of the fifty states, the District of Columbia, and the U.S. territories. Membership is voluntary and includes attorneys in private practice, government service, corporate law departments, and public interest organizations, as well as legislators, law professors, law students, and non-lawyer associates in related fields. ABA members represent the full spectrum of public and private litigants, including plaintiffs and defendants.

The ABA's Section of Intellectual Property Law ("Section") is the world's largest organization of intellectual property professionals, with approximately 19,000 members including lawyers, associates, and law students. In recognition of the importance of patent law, the ABA established the Section in 1894 as the first ABA section to deal with a special branch of the law. The Section has contributed significantly to the development of the American system for the protection of intellectual property rights. The Section is composed of lawyers of diverse backgrounds who represent patent owners, accused infringers, individual inventors, large and small corporations, universities and

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[1] Pursuant to Rule 37.6, *amicus curiae* certifies that no counsel for a party authored this brief in whole or in part and that no person or entity, other than *amicus*, its members, or its counsel, has made a monetary contribution to the preparation or submission of this brief. The parties have consented to the filing of this brief.

Neither this brief nor the decision to file it should be interpreted to reflect the views of any judicial member of the American Bar Association. No inference should be drawn that any member of the Judicial Division Council has participated in the adoption or endorsement of the positions in this brief. This brief was not circulated to any member of the Judicial Division Council prior to filing.

research institutions, all across a wide range of technologies and industries.

At its 2004 Annual Meeting, the ABA House of Delegates adopted a policy that supports appellate review under the *de novo* standard of the ultimate issue of claim construction but which reserves appellate review under the clearly erroneous standard of any underlying findings of fact made by a trial court in connection with construing a claim term.[2] The ABA developed this policy based on its belief that the Federal Circuit's existing practice of reviewing fact-intensive patent claim construction issues without any deference to the district court's findings on the underlying or subsidiary facts does not properly account for complexities inherent in these issues. *See, e.g., Phillips v. AWH Corp.*, 415 F.3d 1303, 1332 (Fed. Cir. 2005) (en banc), cert. denied, 126 S. Ct. 1332 (2006) (Mayer, J., dissenting) ("the nature of the questions underlying claim construction illustrate that they are factual . . . These subsidiary determinations are specific, multifarious and not susceptible to generalization."). One consequence of the Federal Circuit's plenary *de novo* review of these fact-intensive issues, as one would expect, has been a high reversal rate.[3] This high reversal rate has significantly increased the cost of litigation by frequently requiring relitigation of issues following a reversal,[4] or at the

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[2]The ABA House of Delegates' adoption of this position is recorded at http://www.abanet.org/leadership/2004/annual/dailyjournal/302.doc.

[3] *See, e.g.*, Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 Lewis & Clark L. Rev. 231, 232 (2005) (citing 34.5% reversal rate for 1996-2003); *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448, 1476 (Fed. Cir. 1998) (Rader, J., dissenting) (38.3% reversal rate per court's 1997 official statistics).

[4] *See, e.g., Elf Atochem North Am., Inc. v. Libbey-Owens-Ford Co.*, 894 F. Supp. 844, 857, (D. Del. 1995) ("[I]n spite of a trial judge's ruling on the meaning of disputed words in a claim, should a three-judge panel of the Federal Circuit disagree, the entire case could be remanded for retrial on [a] different [claim interpretation].")

very least forcing parties to put in proof and make arguments in the alternative because of the uncertainty of the final claim construction.[5]

The ABA's views on the principle of appellate review of factual conclusions of district courts in patent cases have been developed over a long period of time by practitioners directly involved in these cases. Having had considerable experience with the impact that the Federal Circuit's no-deference rule has had on businesses and individuals across a wide range of technologies and industries, the ABA believes its insights may be of assistance to the Court.

REASONS FOR GRANTING THE PETITION

I. Granting the Petition Will Present an Opportunity for the Court to Provide Needed Guidance on the Proper Role of Appellate Courts When Reviewing Underlying Findings of Fact in Claim Construction Rulings.

This Court in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996), explained that claim construction involves a mixed issue that "falls somewhere between a pristine legal standard and a simple historical fact." *Markman* held that the task of construing claims in the first instance falls to the trial judge, but left open the question of whether an appellate court should give deference to a trial court's findings on underlying or subsidiary facts that might arise in construing the claims. *Id.*, 517 U.S. at 384 n. 10.

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[5] "A Section White Paper: Agenda for 21st Century Patent Reform," ABA Section of Intellectual Property Law, revised February 20, 2007, located at http://www.abanet.org/intelprop/home/PatentReformWP.pdf at 38-39. This White Paper was developed by a task force of experts within the Section to address a number of patent reform issues. The White Paper was reviewed by all sections and divisions of the ABA without objection.

In *Cybor*, the Federal Circuit acknowledged the fact/law dichotomy discussed in *Markman*, but concluded that claim construction is "a purely legal question" it should review "*de novo* on appeal, including any allegedly fact-based questions relating to claim construction." *Cybor*, 138 F.3d at 1456.

The Federal Circuit granted a rehearing *en banc* in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), cert. denied, 126 S. Ct. 1332 (2006), to address several questions, including whether it should "accord any deference to any aspect of trial court claim construction rulings." The court invited briefs *amicus curie*, and the ABA submitted a brief articulating its position that underlying findings of fact should be reviewed under a clearly erroneous standard. Ultimately, the *en banc* panel decided not to resolve this question. *Phillips*, 415 F.3d at 1328.

The *Cybor* approach gives insufficient recognition to the proper competencies of the trial and appellate courts. As this Court has recognized, district courts are better situated to apply fact-dependent legal standards. *See Cooter & Gell v. Hartmarx Corp.*, 496 U.S. 384, 402 (1990) ("Familiar with the issues and the litigants, the district court is better situated than the court of appeals to marshal the pertinent facts and apply the fact-dependent legal standard."); *see also Salve Regina College v. Russell*, 499 U.S. 225, 233 (1991) ("deferential review of mixed questions of law and fact is warranted when it appears the district court is 'better positioned' than the appellate court to decide the issue in question or that probing appellate scrutiny will not contribute to the clarity of legal doctrine"). District court findings on fact-intensive inquiries underlying claim constructions, *Phillips*, 415 F.3d at 1331, should be given deference for precisely these reasons.

These types of concerns led to the amendment of Rule 52(a), Fed. R. Civ. P., in 1985 to make clear that all findings of fact made by the trial court, whether or not they are based on credibility determinations, must be reviewed for clear error. The Advisory Committee explained: "To permit courts of appeals to share more actively in the fact-finding function would tend to undermine the legitimacy of the district courts in the eyes of litigants, multiply appeals by encouraging appellate retrial of some factual issues, and needlessly reallocate judicial authority."

II. *De Novo* Review of Claim Constructions Has Increased Uncertainty and Expense in Patent Litigation.

The *de novo* review of all aspects of claim constructions under *Cybor* has contributed to a substantial reversal rate of district court rulings by the Federal Circuit.[6] Members of the ABA have observed that instead of having the intended effect of "providing national uniformity to the construction of a patent claim," *Cybor*, 138 F.3d at 1455, this approach instead has introduced into patent litigation considerable inefficiencies, unpredictability, and added expense.[7]

A. Appellate Review of Findings of Fact for Clear Error Would Increase Predictability and Reduce Litigation Cost.

Reviewing a district court's ultimate claim construction *de novo* and the underlying findings of fact for clear error will decrease the reversal rate at the Federal

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[6] See note 3 *supra*.

[7] "A Section White Paper: Agenda for 21st Century Patent Reform," ABA Section of Intellectual Property Law, revised February 20, 2007, located at http://www.abanet.org/intelprop/home/PatentReformWP.pdf at 38-39.

Circuit.[8] A lower reversal rate would help reduce patent litigation costs by limiting instances of relitigation and the use of inefficient trial strategies that account for the likelihood of reversal, which in turn would benefit both patentees and accused infringers alike.[9]

B. Affording Deference to Findings of Fact Is Consistent With the Federal Circuit's Goal of Promoting Uniformity in the Patent Law.

Affording deference to underlying findings of fact by a trial court would not impede uniformity. Ultimately, claim construction is a question of law. *Markman*, 517 U.S. at 390. Principles of *stare decisis*,[10] and in some instances issue preclusion, will promote uniformity in circumstances where different district courts are construing the same terms in the same patents. Reviewing underlying questions of fact for clear error will reflect the competencies of the trial and appellate courts and will appropriately allocate judicial resources.

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[8] *Id.*

[9] *Id.*

[10] *See, e.g., Markman*, 517 U.S. at 391 ("treating interpretive issues as purely legal will promote (though it will not guarantee) intrajurisdictional certainty through the application of *stare decisis* on those questions not yet subject to intrajurisdictional uniformity under the authority of the single appeals court.").

CONCLUSION

For the reasons set forth above, the ABA respectfully submits the petition for writ of *certiorari* should be granted.

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Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF CROSS MEDICAL PRODUCTS, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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INTEREST OF THE *AMICUS CURIAE*[1]

Amicus Cross Medical Products, Inc., a subsidiary of Biomet, Inc., is a pioneer for innovation in the orthopedic biomaterials market. Cross holds numerous patents in this field covering, *inter alia*, reconstructive products and fixation devices, and in particular, spinal fixation products. Similarly, Petitioner develops biomedical products, and holds numerous patents covering its innovations. Because of the complex nature of biomedical devices, and because "language remains an imperfect fit for invention," *Festo Corp. v. Shoketsu Kinsoku Kogyo Kabushiki Co.*, 535 U.S. 722, 738 (2002), patent holders in this field particularly rely on the doctrine of equivalents to protect their innovations.

Cross files this *amicus* brief because the Federal Circuit has sharply moved away from this Court's decision in *Festo*, 535 U.S. 722, and has nearly eviscerated the tangentialness exception to prosecution history estoppel. Cross has a vital interest in maintaining its ability to rebut the presumption of estoppel through an appropriate application of that exception. Restoring the test set forth by this Court in *Festo*, 535 U.S. 722, will capture the reality of what takes place during patent prosecution, and will strike the appropriate balance between the patent holder's ability to protect its rights to equivalents and the public's need for notice as to the scope of patent protection.

Like Amgen, Cross has fallen victim to the Federal Circuit's misapplied application of the tangentialness exception to overcoming a presumption of prosecution history estoppel. *See Cross Medical Products, Inc. v.*

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[1] Pursuant to Rule 37.6 of the Rules of this Court, *amicus* states that no counsel for a party has authored this brief, in whole or in part, and that no person or entity, other than *amicus*, its members, or its counsel, has made a monetary contribution to the preparation or submission of this brief. Letters have been filed with the Clerk of the Court confirming that all parties have consented to the submission of this brief.

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Medtronic Sofamor Danek, Inc., No. 05-1415, 2007 WL 817660 (Fed. Cir. Mar. 20, 2007).

Cross, therefore, has a strong interest in urging the Court to grant review and overturn the Federal Circuit's application of its misguided test for rebutting the prosecution history estoppel presumption, and to restore principles previously articulated by this Court. *Amgen Inc. v. Hoechst Marion Roussel, Inc., et al.*, No. 06-1291 provides the opportunity for this Court to immediately end the Federal Circuit's destruction of the balance this Court created.

SUMMARY OF ARGUMENT

Departing from the test for rebutting the presumption of prosecution history estoppel that this Court unanimously announced, and the Federal Circuit interpreted and applied *en banc* less than four years ago, the Federal Circuit has now nearly eviscerated the tangentialness exception to prosecution history estoppel. That exception requires the court to evaluate whether the rationale underlying the amendment bears no more than a tangential relation to the equivalent in question.

While giving lip service to evaluating the rationale for an amendment during prosecution, recently the Federal Circuit has considered whether the *resulting amendment itself*—rather than the *reason* the amendment was made—is related to the equivalent. Because prosecution history estoppel is typically invoked only when features of the alleged equivalent are intertwined with the amended subject matter, it is virtually inevitable that the result of the amendment will relate, in some way, to the alleged equivalent.

Accordingly, the Federal Circuit's new test is virtually, if not completely, insurmountable. It therefore contravenes this Court's mandate that the presumption of estoppel not be a "complete bar by another name." *Festo*, 535 U.S. at 741.

This Court should grant certiorari. The Federal Circuit has destroyed the balance between prosecution history

estoppel and the doctrine of equivalents that this Court established in *Festo.* Restoring that balance is vitally important to the security of patent rights.

ARGUMENT

The Federal Circuit has ignored the principles announced in *Festo Corp. v. Shoketsu Kinsoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), misapplied the test as outlined, and undermined this Court's holding. Review by this Court is urgently warranted.

I. THIS COURT SHOULD GRANT CERTIORARI TO RESTORE PROPER APPLICATION OF LAW THAT HAS BEEN SUBVERTED BY THE FEDERAL CIRCUIT

A. Prosecution History Estoppel As A Limitation On The Doctrine of Equivalents

The doctrine of equivalents is judicial recognition that a patent's scope extends beyond the claim's literal terms to protect an inconsequential variation to a patentable invention. Without the doctrine of equivalents, an "unscrupulous copyist" would be encouraged "to make unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim," rendering patent rights "hollow and useless." *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 607 (1950).

In an effort to clarify the proper scope of the doctrine, this Court identified prosecution history estoppel as a reasonable limitation on the doctrine of equivalents. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 34 (1997). There the Court instructed the Federal Circuit to "consider whether *reasons* for the portion

of the amendment were offered or not and whether further opportunity to establish such *reasons* would be proper," to assess whether that *reason* is sufficient to avoid estoppel. *Id.* (emphasis added). Although the Court provided guidance to the Federal Circuit concerning the scope of the doctrine of equivalents, it declined to "go[] further and micromanag[e] the Federal Circuit's particular word choice for analyzing equivalence." *Id.* at 40. This Court unequivocally *rejected* the notion that an amendment made during patent prosecution categorically surrenders anything beyond the claim's literal terms. *See id.*

More recently, in *Festo*, this Court struck a balance between prosecution history estoppel and the doctrine of equivalents when it ruled that, if a patentee makes a narrowing amendment during prosecution, there is only a *rebuttable presumption* of estoppel. *Festo Corp.*, 535 U.S. at 740. The Court established that a patentee could overcome the presumption that prosecution history estoppel bars the doctrine of equivalents "where the amendment cannot reasonably be viewed as surrendering a particular equivalent." *Id.* The Court set forth specific criteria that must be considered when determining if prosecution history estoppel applies. *Id.* at 740-41.

B. Prosecution History Estoppel Does Not Bar The Doctrine Of Equivalents If The Reason For the Narrowing Amendment Is Tangential To The Accused Equivalent

Acknowledging the importance of the doctrine of equivalents, this Court reasoned that "[a]fter amendment, as before, language remains an imperfect fit for invention," and ruled that "[t]he amendment does not show that the inventor suddenly had more foresight in the drafting of claims than an inventor whose application was granted without amendments

having been submitted." *Festo*, 535 U.S. at 738. Further, this Court recognized that "there is no more reason for holding the patentee to the literal terms of an amended claim than there is for abolishing the doctrine of equivalents altogether and holding every patentee to the literal terms of the patent." *Id.*

The Court then enumerated instances in which prosecution history estoppel would not apply following a narrowing amendment, including where "the rationale underlying the amendment [bears] no more than a tangential relation to the equivalent in question."[2] *Id.* at 740.

After remand, the Federal Circuit, writing *en banc*, explained that the tangentialness criterion "asks whether the reason for the narrowing amendment was peripheral, or not directly relevant, to the alleged equivalent." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1369 (Fed. Cir. 2003) ("*Festo III*"). Thus, this exception "focuses on the patentee's objectively apparent reason for the narrowing amendment." *Id.*

For a short time following this Court's *Festo* decision, the tangentialness test was properly applied to determine whether that exception to prosecution history estoppel had been met. For example, in *Insituform Techs. v. CAT Contracting, Inc.*, the Federal Circuit stated: "The question we must address is 'whether the reason for the narrowing amendment was peripheral, or not directly relevant, to the

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[2] The Court also stated that prosecution history estoppel would not apply to a narrowing amendment when the equivalent was "unforeseeable at the time of the application," or where there was "some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." *Id.* at 740-41. However we not aware of any case where the Federal Circuit applied either the foreseeability test or the rarely invoked residual criterion to rebut prosecution history estoppel. Therefore, the tangential relationship test is the most important *Festo* criterion for maintaining balance between the doctrine of equivalents and prosecution history.

alleged equivalent.'" 385 F.3d 1360, 1370 (Fed. Cir. 2004) (quoting *Festo III*, 344 F.3d at 1365).

Insituform involved a process in which resin was drawn through a tube. The claims, as originally drafted, "would likely have read on a process using . . . multiple [vacuum] cups . . . at any location downstream of the resin . . . ." *Insituform Techs., v. CAT Contracting, Inc.*, 99 F.3d 1098, 1108 (Fed. Cir. 1996). But the claims were amended to avoid the need for a large vacuum compressor at the end of the tube. *Id.* To that end, the amendment added a limitation requiring a single vacuum source located at a point along the tube near the resin. The proximity of the vacuum source to the resin allowed the use of a smaller vacuum. *Id.* Thus, the amended claim was "literally limited to the use of one vacuum cup . . . ." *Id.* at 1108. This claimed design required the single vacuum source to be moved to various positions along the length of the tube as the resin was drawn.

The accused device achieved the same goal as the claimed invention (avoiding the need for a large vacuum compressor at the end of the tube), but did so by placing several vacuums along the length of the tube, each one being removed as the resin was drawn. *Id.* The *Insituform* patentee never indicated that the large vacuum source could be eliminated only in the manner set forth by its added limitation. *Id.*

The Federal Circuit determined that because the *reason* for the amendment was directed towards other prior art, and not the equivalent in question, the amendment and the equivalent were no more than tangentially related, and thus the doctrine of equivalents could apply. *Insituform*, 385 F.3d at 1370. The Federal Circuit appropriately interpreted the scope of the alleged equivalent in *Insituform* to encompass only the *number* of vacuum sources, while the reason for the amendment was to distinguish prior art with respect to the *location* of the vacuum source. *See id.* at 11.

C. The Federal Circuit's Application of The Tangentialness Exception Has Undergone A Transformation And Is Not Consistent With This Court's Precedents

The Federal Circuit has now departed from proper application of the tangentialness test, as outlined in *Festo*, 535 U.S. at 737 and *Festo III*, 344 F.3d at 1369. The Federal Circuit's new rule does not focus on the *reason* for the narrowing amendment, but instead focuses on the *result* of the amendment itself.

In the case presently on petition before this Court, the Federal Circuit has not merely misapplied a properly stated rule of law, but has changed the governing standard for analyzing whether an amendment during prosecution is tangentially related to the alleged equivalent. *Amgen Inc. v. Hoechst Marion Roussel, Inc., et al.*, 457 F.3d 1293, 1313 (Fed. Cir. 2006). In *Amgen*, the court relied on a narrowing amendment that *resulted* in a claim limited to EPO having the "complete 166-amino acid sequence," and concluded that this *result* was determinative of the *reason* for the amendment. The court of appeals brushed aside significant evidence that the actual *reason* for the amendment was "to avoid a double patenting rejection in light of the '933 patent." *Id.* at 1314-15. The court explicitly acknowledged that the limitation added in the preliminary amendment "may have been central to overcoming a double patenting rejection," yet it still relied solely on the *result* of the amendment to conclude that the amendment was not "merely tangential to the alleged 165-amino acid equivalent." *Id.* at 1315. The Federal Circuit specifically signaled its intent to change the legal landscape concerning the doctrine of equivalents when it incorrectly quoted this Court's *Festo* decision for the "narrow ways" to rebut the presumption of prosecution history estoppel. *Id.* at 1310. Nowhere did this

Court ever state, or even imply, that the enumerated methods for rebutting the prosecution history estoppel presumption should be "narrowly" applied.

Similarly, in *Cross Medical Products, Inc.*, 05-1415, 2007 WL 817660, the Federal Circuit committed the same analytical error as it did in *Amgen*. The court of appeals first ascertained the *reason* for the amendment, as it was required to do under this Court's *Festo* decision. *Id.* at *7. But the court of appeals failed to apply the *reason* for this amendment, and—departing from both this Court's precedent and the Federal Circuit's en banc *Festo III* decision—applied the same fundamentally incorrect test as used in *Amgen* for determining whether estoppel was rebutted: Whether the accused equivalent relates to *the result of the amendment itself*. *Id.*

Cross Medical involves a patent that describes a bone screw that is used in spinal surgery. *Id.* at *1. As shown in a figure taken from the patent and reproduced in the court of appeals' opinion itself (shown below), the preferred embodiment of the '555 Patent includes a cap (25) between the compression nut and the rod. *Id.* at *6. In the preferred embodiment, it is this cap, rather than the nut, that contacts the rod. *Id.* at *4.

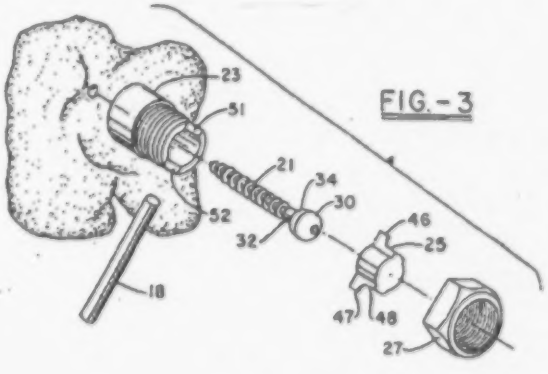

FIG. - 3

All of the original claims of the '555 Patent required the use of a cap. Non-Confidential Joint Appendix, *Cross Medical Products, Inc. v. Medtronic Sofamor Danek, Inc.*, No. 05-1415 at A2284-87 (Dec. 12, 2005). But during prosecution, Cross added additional claims that did not require that a cap be used between the nut and the rod. *Id.* at A2314-18. Claim 5 was one of the claims that was added during prosecution. *Id.*

Claim 5 (originally Claim 15) was rejected, *inter alia*, under 35 U.S.C. § 112 because the claim failed "to provide an enabling description of the embodiment of the action device excluding the cap/cap means." Non-Confidential Joint Appendix, *Cross Medical Products, Inc. v. Medtronic Sofamor Danek, Inc.*, No. 05-1415 at A2327 (Dec. 12, 2005). The claim was amended to add the limitation at issue in *Cross Medical*, which required that the threads of the anchor seat extend towards the bone interface "to a depth below the diameter of the rod." *Cross Medical Products, Inc.*, 05-1415, 2007 WL 817660 at *4. Medtronic, attempting to avoid this limitation, redesigned its bone screw by "'replac[ing] the threads below the top of the rod with a groove or 'undercut.'" *Id.* at *6 (quoting *Cross Medical Products, Inc. v. Medtronic Sofamor Danek, Inc.*, No. SA CV 03-110 GLT (ANx), 2005 WL 5239258 at *3 (Apr. 11, 2005) (unpublished)).

The district court, after examining the *reason* for Cross' amendment, ruled that the rationale was no more than tangentially related to Medtronic's redesigned screws:

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> "The rationale behind the amendment [to claim 5] was to adequately describe and enable a device, under § 112, in which the securing means could secure the rod without the use of a cap. The applicant was not attempting to overcome prior art using an undercut, and the amendment did not relate to an undercut. Therefore, the rationale was no more than tangentially related to Medtronic's new screw design, in which threads extend part of the way toward the rod and an undercut extends to a depth below the top of the rod."

Cross Medical Products, Inc., 05-1415, 2007 WL 817660 at *4 (quoting *Cross Medical Products, Inc.*, 2005 WL 5239258 at *5).

The Federal Circuit credited the district court's reasoning as correct. *Cross Medical Products, Inc.*, 05-1415, 2007 WL 817660 at * 7. The court of appeals agreed that "the patentee narrowed claim 5 to address a § 112 rejection." *Id.* But then, rather than examine if Medtronic's accused equivalent relates to this *reason*, the court instead determined that "the accused equivalent . . . relates to the amendment . . . ," and thus applied prosecution history estoppel. *Id.* ("Thus, the accused equivalent, which does not include threads extending 'to a depth below the top of the stabilizer' and correspondingly does not capture this aspect of the invention *relates to the amendment* as shown even by the applicant's own statements.") (emphasis omitted, emphasis added).

Evidencing the Federal Circuit's sharp departure from this Court's careful balancing in *Festo*, 355 U.S. at 740, the Federal Circuit in *Cross Medical* reaffirmed its new "principle that the tangential relation criterion for overcoming the *Festo* presumption is *very narrow*." *Cross*

Medical Products, Inc., 05-1415, 2007 WL 817660 at *5. (emphasis added).

Further, the basis for the decision in *Cross Medical* could not possibly have been that the *reason* for the amendment relates to the equivalent. The court of appeals ruled that "the prosecution history explains that the thread depth limitation was added to capture the manner in which the stabilizer aspect of the invention operated . . . ." *Id.* at *7. The "stabilizer" is the rod (18), and Medtronic's undercut is completely unrelated to how the rod operates. Medtronic even admitted that the undercut "doesn't change the functionality at all. The thread continues down until it can push against the rod in either case." *Cross Medical Products, Inc. v. Medtronic Sofamor Danek, Inc.*, No. SA CV 03-110 GLT (ANx), 2005 WL 5239258 at *6. Thus, even if the result of the amendment relates to an undercut, *the reason* for the amendment certainly does not.

Underscoring the fact that the Federal Circuit's new "relates to" test is impassable, the Panel supported its decision in *Cross Medical* by noting that "the prosecution history of the '555 patent shows a narrowing amendment that also 'contains the equivalent in question.'" *Cross Medical Products, Inc.*, 05-1415, 2007 WL 817660 at *6 (quoting *Chimie v. PPG Indus. Inc.*, 402 F.3d 1371, 1383 (Fed. Cir. 2005)). But in virtually every case in which prosecution history estoppel is at issue, the narrowing amendment will contain the equivalent in question. That is, after all, the very reason defendants assert prosecution history estoppel.

This test is contrary to both the letter and the spirit of the this Court's decision in *Festo*. This Court ruled that *the rationale* underlying the amendment—not the amendment itself—must bear no more than a tangential relation to the equivalent in question. *Festo*, 355 U.S. at 740. This Court's reasoning in *Festo* clearly envisions that there will be situations in which the result of the amendment is directly

related to the claimed equivalent, but the *reason* for the amendment is no more than tangentially related to the equivalent design. By abandoning that critical distinction between the *scope* of an amendment and the *reasons* for that amendment, the Federal Circuit has effectively embraced the position that this Court explicitly rejected in *Festo*. The court of appeals has created a test for prosecution history estoppel that is effectively insurmountable—thereby contravening this Court's mandate that "[t]his presumption is not, then, just the complete bar by another name." *Id.*, at 741. As the district court in *Amgen* observed, "the correct inquiry is not whether the amendment itself narrows the scope of a claim in a way that affects the equivalent in question. If this were the test, it would be an impassable one—the only reason why the dispute arises is because the equivalent is related to the amendment and affected thereby." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126, 150 (D. Mass. 2003).

Moreover, the "relates to" test that was applied in both *Amgen* and *Cross Medical* cannot be reconciled with the *Festo III* decision, where the Federal Circuit held that "the inquiry into whether a patentee can rebut the Festo presumption under the 'tangential' criterion focuses on the patentee's objectively apparent reason for the narrowing amendment.'" *Festo III*, 344 F.3d at 1369. Indeed, if the test is whether the result of the amendment itself—not the reason for the amendment—"relates to" the equivalent, then there is no need to consider, let alone focus on, the patentee's objectively apparent reason for the narrowing amendment.

The concurring opinion in *Cross Medical* points out that only twice has the Federal Circuit invoked the tangential principle to rebut prosecution history estoppel. *Cross Medical Products, Inc. v. Medtronic Sofamor Danek, Inc.*, No.05-1415, 2007 WL 817660 at * 10 (Judge Rader concurring). After stating that both of those cases "arguably

related to situations where the prosecution history clearly demonstrated that the alleged equivalent and the narrowing amendment implicate entirely different aspects of the invention," the opinion notes that "frankly, this court might well have justifiably reached a different result in both." *Id.* This observation is certainly accurate in light of the test employed in *Cross Medical* and *Amgen*, and highlights the need for review by this Court.

CONCLUSION

Amicus respectfully urges this Court to grant the petition for a writ of certiorari.

Respectfully submitted,

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IN THE
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AMGEN, INC.,
Petitioner,

v.

HOECHST MARION ROUSSEL, INC.
(now known as AVENTIS PHARMACEUTICALS, INC.)
and
TRANSKARYOTIC THERAPIES, INC.
(now known as HUMAN GENETIC THERAPIES, INC.),
Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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STATEMENT OF INTEREST OF *AMICUS CURIAE*

The Federal Circuit Bar Association ("FCBA") is a national organization consisting of approximately 2,400 attorneys whose practice concerns the United States Court of Appeals for the Federal Circuit in all aspects of its jurisdiction. The FCBA offers a forum for dialogue between the bar and the judges of the Federal Circuit. One of the purposes of the FCBA is to submit briefs *amicus curiae* on matters affecting practice before the Federal Circuit and lower tribunals.[1]

Pursuant to Supreme Court Rule 37.2(a), the FCBA has conferred with the parties regarding the filing of this brief *amicus curiae*, and both parties have consented to its filing. Evidence of the written consent of the parties has been filed separately.

The FCBA respectfully submits this brief in support of the Petition for Certiorari filed by Petitioner Amgen Inc. ("Amgen"). The FCBA expresses no opinion on the merits of the underlying legal dispute. It supports Amgen's petition because its members believe that the Federal Circuit's decision in *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) ("*Cybor*") has negatively affected the litigation of patent rights and the patent system as a whole and should be overruled.

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[1] Pursuant to Supreme Court Rule 37.6, the FCBA states that no counsel for a party authored this brief in whole or in part. No person or entity, other than *amicus curiae*, its members, or its counsel, made any monetary contribution to the preparation of the brief.

Counsel for the FCBA in this matter represents Amgen in certain non-litigation matters unrelated to patents. The FCBA notes that its position on the issues addressed in this brief has been a matter of public record for some time. When the Federal Circuit invited briefing on this issue in connection with its *en banc* rehearing of *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), the Federal Circuit Bar Association filed a brief taking precisely the position taken in this brief.

SUMMARY OF ARGUMENT

1. The Supreme Court should grant the Petition for Writ of Certiorari in order to review the Federal Circuit's holding in *Cybor*, followed in this case, that claim construction is subject to *de novo* review. That rule has produced an unacceptably high appellate reversal rate of claim constructions, spawning uncertainty among patent litigants, postponing resolution of patent cases, and discouraging settlement.

2. The Federal Circuit's rationale for *de novo* review rests on the premise that claim construction does not involve determinations of fact. This premise is incorrect, illogical, and inconsistent with this Court's unanimous opinion in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) ("*Markman II*"). Notwithstanding the District Court's assertion that the enormous volume of technical evidence in which it has been immersed during ten years of fact-intensive litigation did not in any way inform its interpretation of the disputed claim terms, the appropriateness of the *Cybor* rule is squarely at issue in this case.

ARGUMENT

This Court should grant certiorari pursuant to Supreme Court Rule 10(c). In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006), the Federal Circuit decided an important question of federal law in a way that conflicts with relevant decisions of this Court. In particular, the Federal Circuit applied its previous decision in *Cybor* that, because claim construction does not rest on determinations of fact, it is a matter of law reserved exclusively for the court, and therefore reviewed *de novo* on appeal.

The Federal Circuit has refused to reconsider *Cybor* despite widespread recognition among practitioners—and even a majority of the Federal Circuit's own judges—that *Cybor* is seriously flawed. In the nine years since the Federal Circuit decided *Cybor*, *de novo* review of claim construction has rendered patent litigation less predictable, spawned unnecessary legal conflict, and discouraged settlement. The FCBA further submits that the requirement of *de novo* review of claim construction rests on an erroneous legal rationale that conflicts with this Court's decision in *Markman II* and with established principles of appellate review embodied in Federal Rule of Civil Procedure 52(a).

For these reasons, the FCBA respectfully requests that this Court review the Federal Circuit's holding in *Cybor* that all aspects of claim construction are subject to *de novo* review.

The FCBA is conscious that this Court relies on the Federal Circuit for the day-to-day development and administration of patent law. *See, e.g., Warner-Jenkinson Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997). However, the FCBA respectfully asks this Court to review the *Amgen* decision because the Federal Circuit is unwilling to revisit the *Cybor* rule *en banc*, notwithstanding

widespread recognition on and off the Federal Circuit that *de novo* review of claim construction has impeded the orderly resolution of patent disputes and rests on an erroneous legal foundation. *See Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (declining to reconsider *Cybor* after requesting briefing on the issue).

I. *DE NOVO* REVIEW OF CLAIM CONSTRUCTION HAS LED TO AN UNACCEPTABLY HIGH REVERSAL RATE, FOSTERING UNPREDICTABILITY, POSTPONING FINALITY, AND DISCOURAGING SETTLEMENT.

Before the Federal Circuit decided *Cybor*, panels of that court routinely acknowledged that claim construction was firmly rooted in factual inquiry. For example, the Federal Circuit counseled in one of the leading pre-*Markman* cases that "[i]n a patent case involving complex scientific principles, it is particularly helpful to see how those skilled in the art would interpret the claim." *Moeller v. Ionetics, Inc.*, 794 F.2d 653, 657 (Fed. Cir. 1986). Although the *Moeller* court could not say that eliciting expert testimony from those skilled in the art was "a requirement in all cases," it nevertheless concluded that "the trial judge's failure to allow such testimony was an abuse of discretion." *Id. See also Palumbo v. Don-Joy Co.*, 762 F.2d 969, 976 (Fed. Cir. 1985) ("[W]hen the meaning of a term in the claim is disputed and extrinsic evidence is necessary to explain that term, then an underlying factual question arises, and construction of the claim should be left to the trier or jury under appropriate instruction."); *Bio-Rad Lab., Inc. v. Nicolet Instrument Corp.*, 739 F.2d 604, 613 (Fed. Cir. 1984) (The issue of infringement turned on "whether reasonable jurors, after reviewing all the evidence, could have

interpreted the claims to include" the allegedly infringing activity.).[2]

When the Federal Circuit ruled in *Cybor* that claim construction was subject to *de novo* review, it was with the expectation that plenary review would promote greater predictability, and therefore early settlement, by providing finality with respect to the meaning of litigated claims. Concurring in *Cybor*, Judge Plager observed, "[o]ur purpose is to improve the process of patent infringement litigation for the benefit of patentees and their competitors, and ultimately the public." *Cybor*, 138 F.3d at 1463. Whether the "new regime" would prove beneficial "in the long run" remained to be seen, Judge Plager acknowledged, "[b]ut it may be some time before we have enough experience with 'Markman hearings' and with [*de novo*] appellate review to draw any empirically sound conclusions." *Id.*

Our members have now litigated patent claims under the *Cybor* rule for nine years. As the result of this experience, the FCBA has concluded that, not only has *de novo* review of claim construction failed to "improve the process of patent litigation"; it has spawned an unacceptably high reversal rate and, with it, endemic uncertainty among

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[2] As these statements suggest, the interpretation of disputed claim terms was often assigned to the jury. *See, e.g., Tol-O-Matic, Inc. v. Proma Produkt-Und Mktg.*, 945 F.2d 1546, 1552 (Fed. Cir. 1991) ("When the question of infringement turns on the interpretation of the claim, we review whether a reasonable jury could have interpreted the claim in a way that supports its finding on the question of infringement."); *McGill, Inc. v. John Zink Co.*, 736 F.2d 666, 672 (Fed. Cir. 1984) (In the event that "the meaning of a term of art in the claims is disputed and extrinsic evidence is needed to explain the meaning, construction of the claims could be left to a jury."). *See also* William H. Burgess, Comment: *Simplicity at the Cost of Clarity: Appellate Review of Claim Construction and the Failed Promise of Cybor*, 153 U. Pa. L. Rev. 763, 769-71 (2004) (describing the "mixed standard of review" employed by the Federal Circuit in the pre-Markman era). The Federal Circuit Bar Association does not suggest that claim construction should be a matter for the jury.

litigants and practitioners.[3] This conclusion is well supported by empirical data. Scholarly analyses of the Federal Circuit's post-*Markman II* review of claim constructions place the reversal rate between 35% and 44%.[4] Further, although the reversal rate did begin to decline in the wake of *Markman II*, it rose in each of the five years following the Federal Circuit's decision in *Cybor*.[5]

As a result, *Cybor* has produced the opposite of its desired effect. Far from encouraging authoritative early construction of patent claims, *de novo* review instead defers

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[3] Dissenting in the Federal Circuit's denial of rehearing *en banc*, Chief Judge Michel identified four practical problems with the *Markman-Cybor* regime:

> (1) a steadily high reversal rate; (2) a lack of predictability about appellate outcomes, which may confound trial judges and discourage settlements; (3) loss of the comparative advantage often enjoyed by the district judges who heard or read all of the evidence and may have spent more time on the claim construction than we ever could on appeal; and (4) inundation of our court with the minutia of construing numerous disputed claim terms (in multiple claims and patents) in nearly every patent case.

Amgen, Inc. v. Hoechst Marion Roussel, Inc., 469 F.3d 1039, 1040 (Fed. Cir. 2006) (Michel, C.J., dissenting).

[4] *See* Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 Lewis & Clark L. Rev. 231, 233 (2005) (35%); Christian A. Chu, *Empirical Analysis of the Federal Circuit's Claim Construction Trends*, 16 Berkeley Tech. L.J. 1075, 1104 (2001) (44%); Gretchen Ann Bender, *Uncertainty and Unpredictability in Patent Litigation: The Time is Ripe for a Consistent Claim Construction Methodology*, 8 J. Intell. Prop. L. 175, 207 (2001) (40%). As then-Professor Moore noted, the two latter studies do not account for the Federal Circuit's Rule 36 summary affirmances. Moore, *supra*, at 234. *See also Cybor*, 138 F.3d at 1476 (Rader, J., dissenting) (noting that the Federal Circuit reversed in whole or in part 53% of appealed claim constructions, according to the Federal Circuit's official 1997 statistics, and citing studies showing a 40% reversal rate for claim construction since *Markman I*).

[5] *Id.* at 246.

until the appellate decision the point at which litigants and practitioners can reliably assess their likelihood of prevailing. At that point, the opportunity for early resolution is long past. As Judge Rader explains, the "Markman I regime means that the trial court's early claim interpretation provides no early certainty at all, but only opens the bidding. The meaning of a claim is not certain until nearly the last step in the process—decision by the Court of Appeals for the Federal Circuit." *Cybor*, 138 F.3d at 1476 (Rader, J., dissenting). One district judge candidly explained that "lawyers know litigation will be a long haul because what the district court says ultimately will not determine the issue." Hon. Kathleen M. O'Malley, Hon. Patti Saris, and Hon. Ronald H. White, *The Past, Present and Future of the Federal Circuit: A Panel Discussion: Claim Construction from the Perspective of the District Judge*, 54 Case W. Res. L. Rev. 671, 682 (2004) (statement of Judge Saris).[6] Another district judge cited a fear among practitioners that the Federal Circuit's high reversal rate induced trial judges to grant summary judgment even when there are disputed facts, reasoning, "I do not want to try this case twice, [so I'll] just send it up. Let the Federal Circuit tell me whether I got the claim construction wrong by making the infringement decision on the summary judgment." *Id.* at 687 (statement of Judge O'Malley).[7]

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[6] Judge Saris went on to note a recent increase in preliminary injunction motions in patent cases, "so that parties can appeal . . . and get a quick read on the claim construction. . . . Patent litigators want to get that claim construction up to the CAFC." *Id.* Judge Rader has similarly observed that as a result of the high reversal rate, "the trial court becomes a ticket to the real center stage, the Court of Appeals for the Federal Circuit." *Cybor*, 138 F.3d at 1476 (Rader, J., dissenting).

[7] This dynamic unnecessarily taxes judicial resources and contributes to the spiraling cost of patent litigation. The American Intellectual Property Law Association reports that the average cost of litigating a patent infringement suit when more than $25 million is at stake surged from less than $3 million in 2001 to $4.5 million in 2005—an increase of

This case presents an important opportunity to stem the rising reversal rate and promote greater predictability in, and earlier resolution of, patent cases. On account of these important pragmatic considerations alone, this Court should grant Amgen's Petition for Certiorari.

II. THE FEDERAL CIRCUIT'S RATIONALE FOR *DE NOVO* REVIEW OF CLAIM CONSTRUCTION IS LEGALLY INCORRECT AND INCONSISTENT WITH THIS COURT'S UNANIMOUS OPINION IN *MARKMAN II*

A. The Federal Circuit's Rationale for *De Novo* Review Rests on the Faulty Premise that Claim Construction Does not Involve Determinations of Fact

When a trial court construes a disputed claim term, "the focus is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 986 (Fed. Cir. 1995) ("*Markman I*"). As this Court and several judges on the Federal Circuit have observed, this is an inherently factual inquiry. During Markman hearings, "which are often longer than jury trials," explained Judge Mayer, parties vigorously dispute

> who qualifies as one of ordinary skill in the art; the meaning of patent terms to that person; the state of the art at the time of the invention; contradictory dictionary definitions and which would be consulted by the skilled artisan; the scope of specialized terms; the problem a patent was solving; what is related or pertinent art; whether a construction was disallowed during

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more than 50% in just four years. American Intellectual Property Law Association, *Report of the Economic Survey 2005* 23 (2005).

> prosecution; how one of skill in the art would understand statements during prosecution; and on and on.

Phillips, 415 F.3d at 1333 (Mayer, J., dissenting from the denial of rehearing *en banc*).

To patent practitioners, it is uncontroversial to assert that claim construction often requires the trial court to resolve underlying issues of fact. However, the *Cybor* rule perpetuates a fiction: that trial courts rely on extrinsic evidence only to understand the technology, but not to determine the meaning of claims. As the Federal Circuit declared in *Markman I*, while extrinsic evidence

> may be necessary to inform the court about the language in which the patent is written[,] . . . [it] is not for the purpose of clarifying ambiguity in claim terminology. It is not ambiguity in the document that creates the need for extrinsic evidence but rather the unfamiliarity of the court with the terminology of the art to which the patent is addressed.[8]

Markman, 52 F.3d at 986. *See also Cybor*, 138 F.3d at 1454.

This rationale defies experience and common sense. Trial judges routinely hear many hours of expert testimony and review extensive documentary evidence in the course of determining how a person of ordinary skill in the art would have interpreted a claim term at the time of the invention. In the present case, as Chief Judge Michel explained, the District Court's claim construction was "well grounded in . . . evidence" gleaned from 32 days of trial, "extensive findings of fact and conclusions of law," and tutorials from an M.I.T. Professor whom the District Court appointed as a technical advisor. *Amgen*, 457 F.3d at 1318 (Michel, C.J.,

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[8] The Federal Circuit's exceptionally high reversal rate for claim construction, *see supra*, belies its assertion in *Markman I*, *Cybor*, and *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576 (Fed. Cir. 1996), that claim terms themselves typically are not ambiguous and thus can be interpreted on the basis of the intrinsic record alone.

dissenting).[9] Rarefied theoretical distinctions between understanding the technology and clarifying ambiguity in claim terminology notwithstanding, determining the meaning of a disputed term to a person of ordinary skill in the art at the time of invention is an inherently factual enterprise.[10]

As recently as 2005, the Federal Circuit refused to revisit the *Cybor* rule *en banc*, even after requesting briefing from the parties on whether it is "appropriate . . . to accord any deference to any aspect of trial court claim construction rulings." *Phillips*, 415 F.3d at 1328. Because the Federal Circuit has inexplicably refused to revisit *Cybor* despite the inclination of many of its judges to do so,[11] and because the

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[9] *See also Phillips*, 415 F.3d at 1334 (Mayer, J., dissenting) ("In order to reconcile the parties' inconsistent submissions and arrive at a sound interpretation, the district court is required to sift through and weigh volumes of evidence.").

[10] The Federal Circuit's admonition that, in construing patent claims, trial courts typically can and should eschew "extrinsic" evidence in favor of the "intrinsic" record, is premised on an implausibly categorical distinction between "extrinsic" and "intrinsic" evidence. Specifically, the Federal Circuit cordons off evidence that is included within the patent's file history—the claim, specification, and prosecution history—and labels it "intrinsic," on the theory that such evidence constitutes the "public record" of the patented invention. *Vitronics*, 90 F.3d at 1584. But why should a court's reliance on prior art that is part of the file history to define the scope of a claim qualify as pure legal construction, while its consideration of other prior art constitutes fact-finding? Yet it is this bright-line distinction that the Federal Circuit invokes to support its position that claim construction is devoid of fact-finding.

[11] In this and other cases, at least five of the twelve sitting Federal Circuit judges have directly criticized *de novo* review of claim constructions. *See, e.g., Amgen*, 469 F.3d at 1040 (dissent of Judge Michel, joined by Judge Rader); *id.* at 1041 (dissent of Judge Newman); *id.* at 1044 (dissent of Judge Rader); *id.* at 1045 (dissent of Judge Moore); *Cybor*, 138 F.3d at 1463-66 (concurrence of Judge Mayer, joined by Judge Newman); *id.* at 1473-73 (dissent of Judge Rader, joined by Judge Newman); *id.* at 1478-81 (additional views of Judge Newman, joined by Judge Mayer); *Phillips*, 415 F.3d at 1330-34 (dissent of Judge Mayer, joined by Judge Newman). At least four others have implied dissatisfaction with *de novo* review, *Amgen*, 469 F.3d at 1043

Cybor rule undermines the orderly and timely resolution of patent cases, this Court should grant the Petition for Certiorari.

B. *De Novo* Review of Claim Construction is Inconsistent with *Markman II*

In *Markman II*, this Court concluded that, by virtue of judges' "training and discipline," they, rather than juries, are best positioned to undertake the kind of highly technical and time-consuming analysis that often is required to construe a patent claim. The decision hinged not on "history" or "precedent," but on "functional considerations" of the respective institutional competencies of judges and juries to "define terms of art." *Markman II*, 517 U.S. at 388. This Court explained:

> The decisionmaker vested with the task of construing the patent is in the better position to ascertain whether an *expert's proposed definition* fully comports with the specification and claims and so will preserve the patent's internal coherence. We accordingly think there is sufficient reason to treat construction of terms of art like many other responsibilities we cede to a judge in the normal course of trial, *notwithstanding its evidentiary underpinnings*.

Markman II, 517 U.S. at 390 (emphasis added).

Three points bear special emphasis. First, this passage explicitly recognizes the "evidentiary underpinnings" of claim construction. Second, this Court presumes that, in the course of construing a claim, judges will weigh the "proposed definition[s]" of experts. Third, the passage

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(concurrence of Judge Laurie), or indicated a willingness to reconsider certain aspects of *Cybor*. *See, e.g.*, *id.* at 1045 (concurrence of Judge Gajarsa, joined by Judges Linn and Dyk); *Phillips*, 415 F.3d at 1330 (dissent of Judge Lourie).

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highlights the practical, rather than legal, reasons to allocate claim construction to the court. Claim construction falls to judges not because it is a purely legal activity, but because it is best performed by a judge.

Notwithstanding the pragmatism of *Markman II*, the Federal Circuit has taken this Court's pronouncement that claim construction is a matter for the court, stripped it of its context, and declared that claim construction is a pure matter of law that must be reviewed *de novo*. In so doing, the Federal Circuit has overlooked this Court's repeated acknowledgement in *Markman II* that claim construction is fact-dependent.[12] Judge Newman noted the inconsistency between the Federal Circuit's approach and this Court's opinion in her dissent in *Cybor*:

> In *Markman [I]* the *en banc* court took the position that in patent cases, unlike any other area of law, a disputed question of the meaning, scope, and usage of terms of technologic art is not a question of fact, or even of law based on underlying fact, but is pure law. However, the Supreme Court has relieved us of adherence to this fiction, by its recognition of the factual component of claim interpretation. Further, the Court's affirmation that claim interpretation "is exclusively within the province of the court," [citation omitted], did not shut out the trial judge along with the jury.

Cybor, 138 F.3d at 1480 (Newman, J., offering "additional views"). This Court should therefore grant certiorari in order

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[12] As the Petitioner and several Federal Circuit judges have observed, this Court noted throughout *Markman II* that claim construction was in fact a "mongrel practice," *Markman II*, 517 U.S. at 390, that "falls somewhere in between a pristine legal standard and a simple historical fact." *Id.* at 388.

to assess the compatibility of the *Cybor* rule with its opinion in *Markman II*.

C. Notwithstanding the District Court's Purported "Disavowal" of Reliance on Factual Determinations, the Appropriateness of the *Cybor* Rule is Ripe for Review

Respondents contend that this Court should deny certiorari on the ground that, because the District Court's claim construction did not "rest on any 'findings of fact,'" the appropriateness of the *de novo* standard of review applied by the Federal Circuit is not at issue. Resp. at 1. They refer, in particular, to Judge Young's repeated "disavowal" that he relied on extrinsic evidence in construing the claim. Respondents misunderstand the District Court's opinion.

The Federal Circuit instructs trial judges that they may resort to extrinsic evidence, including prior art and expert testimony, to understand the technology embodied in the patent, but not to interpret the scope of a patent claim. If that distinction strikes this Court as conceptually difficult, consider it from the perspective of a judge who has benefited from the tutorials of a technical advisor, heard testimony from multiple experts, reviewed reams of documentary evidence, and presided over hundreds of trial hours. "What happens when that learning influences a trial judge's interpretation of the claim terms?" asks Judge Rader. "Are trial judges supposed to disguise the real reasons for their interpretation?" *Cybor*, 138 F.3d at 1474 (Rader, J., dissenting).

While Judge Young indicated in his opinion that the extensive technical education he received during the course of the litigation did not inform his interpretation of the disputed claim term, his opinion also suggests that such professions may represent little more than a compulsory nod to the *Cybor* rule. Judge Young described an "apparent

conundrum" created by the Federal Circuit's extrinsic evidence rule:

> [I]t discourages resort to extrinsic evidence while at the same time urging courts to begin claim construction by considering the plain and customary meaning of a term as understood by one skilled in the art. How does a Court decipher the plain and customary meaning of a term as understood by one skilled in the art without resorting to extrinsic evidence about how one skilled in the art would construe the term?

Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202, 226 n.23 (D. Mass. 2004).

Judge Young appeared skeptical about the plausibility of simply "drawing a line between cognitive and investigative tasks," *see id.*, but ultimately concluded: "The Federal Circuit has decided, however, that . . . [t]he task of claim construction falls on the 'cognitive' side of the divide between expanding and applying cognitive capacities, on the one hand, and investigating facts, on the other." *Id.* Therefore, he characterized his construction of the disputed term as the product of a purely legal analysis of intrinsic evidence. As Judge Rader remarked of Judge Young's opinion, "[d]istrict court judges have learned to disclaim any reliance on expert testimony." *Amgen*, 469 F.3d at 1044 (Rader, J., dissenting).[13]

The Federal Circuit defines what district courts do when they construe patent claims as a purely legal exercise that is unburdened by extrinsic evidence. Because district judges, including Judge Young, are mindful of this jurisprudence and draft their claim construction opinions accordingly, it is unreasonable to expect any claim

[13] We might also ask, as Judge Rader did in *Cybor*, "[h]ow will this perverse incentive to 'hide the ball' improve appellate review?" *Cybor*, 138 F.3d at 1474 (Rader, J., dissenting).

construction opinion to pose an explicit challenge to *Cybor*, regardless of its actual basis. For this reason, the *Cybor* regime will continue without review unless this Court looks past the District Court's characterization of its approach to consider instead how the Judge Young actually determined what the disputed claim term meant to a person skilled in the art at the time of the invention. In short, an objective reading of the District Court's opinion indicates that the *Cybor* rule is ripe for review.

CONCLUSION

For the foregoing reasons, amicus curiae Federal Circuit Bar Association respectfully requests that this Court grant the Petition for Writ of Certiorari.

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AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF *AMICUS CURIAE* OF THE SAN DIEGO INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF PETITIONER

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I. THE INTEREST OF THE *AMICUS CURIAE*[1]

The *Amicus Curiae*, the San Diego Intellectual Property Law Association ("SDIPLA"), is a non-profit organization comprising a representative cross-section of individuals in San Diego County with an interest in intellectual property law. Its membership is drawn from patent attorneys and agents who address patent issues on behalf of companies, institutions, and inventors. SDIPLA members represent both owners and users of intellectual property. The San Diego region is home to a significant share of the nation's telecommunications, biotechnology and pharmaceutical companies, and a number of research institutions, including the University of California at San Diego, Salk, Scripps, and the Burnham Institute.

A 2004 study ranked San Diego first among U.S. biotechnology centers, based on two broad categories: the innovation pipeline (the infrastructure that allows a region to capitalize on its biotech knowledge and creativity) and the current impact assessment (an area's success in bringing ideas to the marketplace and creating companies, jobs and products). *See* Skip Rimer, *Study Ranks San Diego #1 Among U.S. Biotech Centers*, Biotechnology News, June 17, 2004, at I-2.

The SDIPLA has no stake in any of the parties to this litigation or the result of this case, other than its interest in seeking correct and consistent interpretation of the law affecting intellectual property and the enforcement and defense of intellectual property rights.

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[1] No counsel for any party authored this brief either in whole or in part, and no persons other than the *Amicus Curiae* and its counsel made any monetary contribution to its preparation or submission. The parties' written consents to the filing of this brief have been filed with the Clerk of the Court.

II. SUMMARY OF ARGUMENT

The SDIPLA respectfully submits this brief in support of petitioner, Amgen Inc., urging the grant of a petition for writ of *certiorari* to review the judgment of the United States Court of Appeals for the Federal Circuit. The Federal Circuit's judgment fails to give appropriate deference to the trial court's evidentiary findings underlying its legal conclusions on claim construction and the application of prosecution history estoppel to the Doctrine of Equivalents, and additionally fails to apply the appropriate test under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), for determining whether the patentee rebutted the presumption of surrender of equivalents.

The interest of the *Amicus* is in ensuring that the appellate standard of review for factual findings underlying claim construction properly allocates judicial resources, and appropriately weighs the public interest in certainty in patent practice that would be promoted if the Court of Appeals accorded deference to the trial court as the finder of the facts. To continue *de novo* review of these factual findings will perpetuate a high reversal rate; tend to undermine the legitimacy of the district courts in the eyes of patent litigants, multiply appeals by encouraging appellate retrial of factual issues, delay settlements until appellate resolution, and needlessly duplicate and reallocate judicial authority. The Court's guidance is therefore needed to ensure that the trial on the merits is the "main event," not just a "tryout on the road" to the Federal Circuit. *See Wainwright v. Sykes*, 433 U.S. 72, 90 (1977).

The Federal Circuit's unwillingness to acknowledge the evidentiary underpinnings of claim construction have also forced trial courts to disclaim reliance on extrinsic evidence that could inform the court's understanding of the meaning of technical terms to one of ordinary skill in the art. In view of these difficulties with the Federal

Circuit's *de novo* review standard, the SDIPLA therefore urges the granting of *certiorari* and a holding that the District Court should find facts necessary for claim construction.

A further interest of the SDIPLA is to preserve the flexibility of this Court's rule governing rebuttal of the presumption of surrender of equivalents under *Festo*. This Court has previously determined that advancing appropriate incentives for innovation warrants application of a "flexible rule" to determine if a patentee has rebutted the presumption of surrender of equivalents. Additional direction from this Court on the proper formulation of the "tangential relation" test, and whether appellate review includes deference to underlying factual findings is thus necessary to prevent resurrection of a rigid bar to infringement under the doctrine of equivalents.

The Court's decision whether to grant *certiorari* will therefore have far ranging effects on appellate review of trial court rulings in patent cases, and in ensuring appropriate incentives for innovation.

III. ARGUMENT

A. THE FEDERAL CIRCUIT'S *DE NOVO* REVIEW OF THE EVIDENTIARY UNDERPINNINGS OF CLAIM CONSTRUCTION SHOULD BE OVERRULED

At issue in this case is the standard of review of factual findings underlying patent claim construction. *See Markman v. Westview Instruments Inc.*, 517 U.S. 370 (1996).

This Court's lodestar ruling in *Markman* has indelibly altered the course of patent litigation. Yet, in the decade since this Court pronounced that the trial court is the

proper arbiter of claim construction, the Federal Circuit has wrestled with its standard of review for fact findings underlying claim construction, and further, the extent to which the trial court may base its claim construction on extrinsic evidence. *See, e.g., Cybor Corp. v. FAS Techs. Inc.*, 138 F.3d 1448 (Fed. Cir. 1998); *see also id.* at 1462 (Plager, J., concurring); *id.* at 1464 (Mayer, C.J., and Newman, J., concurring); *id.* at 1473-75 (Rader, J., dissenting in part); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1040-41 (Fed. Cir. 2006) (denying *reh'g en banc*) ("*Amgen V*") (Michel, C.J., and Rader, J., dissenting); *id.* at 1043 (Newman, J., dissenting); *id.* at 1044 (Rader, J., dissenting); *id.* at 1046 (Moore, J., dissenting). Even though the *en banc* panel of the Federal Circuit settled on *de novo* review in *Cybor*, the debate has continued. *See, e.g., Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*) (noting the order granting rehearing *en banc* requested parties to brief the issue of whether to accord deference to any aspect of trial court claim construction rulings, but deciding not to address the issue).

Because claim construction is the first step in the analysis of patent infringement and invalidity, claim construction is the centerpiece for any patent litigation. Indeed, this Court has recognized that victory in a patent lawsuit turns on whether a patent claim covers "the alleged infringer's product or process," which requires a determination of "what the words in the claim mean." *Markman*, 517 U.S. at 374 (quoting H. Schwartz, Patent Law and Practice 80 (2d ed. 1995)).

Litigants and trial courts undertaking the odyssey of determining claim construction from the vantage of one of ordinary skill in the art, however, are caught between the Scylla of resorting to expert testimony and other extrinsic evidence to inform the court of the meaning of claim terms to one of ordinary skill in the art, and the Charybdis of the Federal Circuit's *de novo* review, and Spartan view of

circumstances when reliance on extrinsic evidence is proper. *E.g.*, *Phillips*, 415 F.3d at 1330 ("We have viewed extrinsic evidence in general as less reliable than the patent and its prosecution history in determining how to read claim terms, for several reasons."); *see also Amgen V*, 469 F.3d at 1040-41 (Michel, C.J., and Rader, J., dissenting) ("It seems to me that the claim construction question often cannot be answered without assessing . . . what the average artisan knew and how she thought about the particular technology when the patent claims were written . . . Indeed, trial judges are arguably better equipped than appellate judges to make these factual determinations"); *Cybor*, 138 F.3d at 1476 (Rader, J., dissenting) (noting the Federal Circuit's high reversal rate, attributed to that court's free review of claim construction).

In the eight years following *Markman*'s allocation of claim construction to the court, the Federal Circuit held that the district court erred in construing 34.5% of claim terms. *See* Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?* 9 LEWIS & CLARK L. REV. 231, 239 (2005) (evaluating cases from 1996-2003). That reversal rate rose further after *Cybor*'s ruling that even "allegedly fact based questions relating to claim construction" were to be reviewed *de novo*. *See id.* at 246.

Thus, clarification by this Court that the standard for appellate review of a trial court's claim construction should require deference to underlying evidentiary findings will provide greater certainty in patent practice, promote greater confidence in the court system and properly allocate judicial resources.

1. This Court Has Recognized that Claim Construction Is Based on Factual Underpinnings

Although this Court ruled in *Markman* that the trial court judge's trained ability to evaluate expert testimony in relation to the overall structure of the patent outweighed the jury's forte in determining witness credibility, it reached its decision to cede claim construction to the judge "notwithstanding its evidentiary underpinnings." *Markman*, 517 U.S. at 390.[2] The Court further explained that the "mongrel" issue of construing a term of art following receipt of evidence did not lend itself to a simple line drawing between "issues of fact and law." *Id.* at 378. Instead, the Court looked to whether the judge or the jury was best suited to address the mixed issue of claim construction, falling somewhere between a "pristine legal standard and simple historical fact." *Id.* at 388 ("[J]udges, not juries, are better suited to find the acquired meaning of patent terms.").

2. The Facts Underlying Claim Construction Should Be Reviewed with Deference

Despite the Court's recurring characterization of claim construction as a mixed issue of law and fact, the Federal Circuit held that *Markman* did not compel deferential appellate review of factual findings underlying claim interpretations, concluding instead that "[n]othing in the

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[2] The Court also noted that allocating claim construction to the court would promote intrajurisdictional certainty; however, even different panels of the Federal Circuit have reached different claim constructions on different records. *See CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1157-58, 1160 n.7 (Fed. Cir. 1997) (finding error in claim construction affirmed in an earlier appeal from ruling on motion for preliminary injunction), *cert. denied*, 118 S.Ct. 1039 (1998).

Supreme Court's opinion supports the view . . . that claim construction may involve subsidiary or underlying questions of fact." *Cybor*, 138 F.3d at 1455. By relegating the Court's characterizations of claim construction to the status of "prefatory comments" and holding that claim construction was "purely legal," the *Cybor en banc* panel sidestepped reconciling its *de novo* standard of review with Federal Rule of Civil Procedure 52(a)'s mandate that factual findings be reviewed under a "clearly erroneous" standard, and further failed to accommodate "the respective institutional advantages of trial and appellate courts." *See, e.g., Anderson v. City of Bessemer*, 470 U.S. 564, 574-75 (1985) (Rule 52(a) requires fact findings to be reviewed with deference); *Salve Regina College v. Russell*, 499 U.S. 225, 233 (1991) ("Those circumstances in which Congress or this Court has articulated a standard of deference for appellate review of district-court determinations reflect an accommodation of the respective advantages of trial and appellate courts."). The ruling in *Cybor* also ignores inconsistencies that could result if the level of ordinary skill in the art is reviewed *de novo* for claim construction, but with deference for other patent law issues.

(a) Federal Rule of Civil Procedure 52(a) Mandates that Trial Court Factual Findings Be Reviewed with Deference

This Court has staunchly held that deferential review of trial court factual findings pursuant to Federal Rule of Civil Procedure 52(a) is the rule, rather than exception. *E.g., Anderson*, 470 U.S. at 574-75; *Inwood Labs., Inc. v. Ives Labs., Inc.*, 456 U.S. 844 (1982); *cf. Bose Corp. v. Consumers Union*, 466 U.S. 485 (1984) (holding that compelling constitutional concerns and line of First Amendment Supreme Court case law warranted finding exception for standard of review of "malice").

"To permit courts of appeals to share more actively in the fact-finding function would tend to undermine the legitimacy of the district courts in the eyes of litigants, multiply appeals by encouraging appellate retrial of some factual issues, and needlessly reallocate judicial authority." Fed. R. Civ. P. 52(a), Advisory Committee Notes to the 1985 Amendment (discussing justification for deferential review of factual findings, including those based on documentary evidence). Deferential review of fact findings avoids duplication and "diversion of judicial resources" even when the factual findings are not based on determinations of credibility. *See Anderson*, 470 U.S. at 574-75. The conclusiveness of a finding of fact, however, depends on the nature of the evidence supporting the finding and whether the fact is a historical fact or ultimate fact; for example, fact findings based on determinations of witness credibility may be entitled to a greater presumption of deference under Rule 52(a). *Bose Corp.*, 466 U.S. at 500-01 & n.16. The deference accorded fact findings may further depend on the length and complexity of the trial court proceeding:

> [T]he standard does not change as the trial becomes longer and more complex, but the likelihood that the appellate court will rely on the presumption tends to increase when trial judges have lived with the controversy for weeks or months instead of just a few hours.

Id. at 500.

Consistent with these principles, several judges writing separately to concur in the majority opinion in *Cybor* supported deferential review of the trial court's fact findings. *See, e.g., Cybor*, 138 F.3d at 1462 (Plager, J., concurring) ("Though we review that record 'de novo,' meaning without applying a formally deferential standard of review, common sense dictates that the trial judge's view will carry weight. That weight may vary depending on the care, as shown in the record, with which that view

was developed, and the information on which it was based."); *id.* at 1463 (Bryson, J., concurring) ("Simply because a particular issue is denominated a question of law does not mean that the reviewing court will attach no weight to the conclusion reached by the tribunal it reviews . . . What it means is that we approach the legal issue of claim construction recognizing that with respect to certain aspects of the task, the district court may be better situated than we are, and that as to those aspects we should be cautious about substituting our judgment for that of the district court."); *id.* at 1464 (Mayer, C.J., and Newman, J., concurring) ("Wisely, the Supreme Court stopped short of authorizing us to find facts *de novo* when evidentiary disputes exist as part of the construction of a patent claim and the district court has made these findings without committing clear error."). Unlike statutory construction, the facts underlying the interpretation of a patent relate to the level of skill in the technology and the understanding of one of skill in the art. *See, e.g.*, *Amgen V*, 469 F.3d at 1040-41 (Michel, C.J., and Rader, J., dissenting). Accordingly, the factual findings relevant to claim construction should be reviewed with deference, in accordance with the principles underlying Rule 52(a).

(b) The Trial Court Is Better Positioned to Make Factual Findings on Claim Construction

This Court has further advised that the respective advantages of trial and appellate court determinations should be weighed in determining whether the appellate court should defer to a trial court's factual findings:

> The Court counsels appellate courts to defer "when it appears that the district court is 'better positioned' than the appellate court to decide the issue in question or that probing appellate scrutiny will not contribute to the clarity of legal doctrine."

> *Salve Regina College v. Russell*, 499 U.S. 225, 233 (1991). At another point, the Court cautions: "[T]he reviewing attitude that a court of appeals takes toward a district court decision should depend upon 'the respective institutional advantages of trial and appellate courts.'" *First Options of Chicago, Inc. v. Kaplan*, 514 U.S. 938, 948 (1995) (quoting *Salve Regina*, 499 U.S. at 233).

Cybor, 138 F.3d at 1477 (Rader, J., dissenting from the pronouncements on claim interpretation); *see also Amgen V*, 469 F.3d at 1040-41 (Michel, C.J., and Rader, J., dissenting) (noting that trial judges are arguably better equipped than appellate judges to make fact findings related to claim construction). The trial court in a patent proceeding is better positioned than the Federal Circuit to acquire and evaluate testimonial evidence, and has more time to devote to review of documentary evidence pertinent to claim construction:

> Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, examining on site the operation of the principles of the claimed invention, and deliberating over the meaning of the claim language. If district judges are not satisfied with the proofs proffered by the parties, they are not bound to a prepared record but may compel additional presentations or even employ their own court-appointed expert.

Cybor, 138 F.3d at 1477 (Rader, J., dissenting). Finally, it is unfair to litigants to force them to retry underlying facts to an appellate court ill-suited to acquire factual evidence:

> In addition, the parties to a case on appeal have already been forced to concentrate their energies and resources on persuading the trial judge that

> their account of the facts is the correct one; requiring them to persuade three more judges at the appellate level is requiring too much. As the Court has stated in a different context, the trial on the merits should be "the 'main event' . . . rather than a 'tryout on the road.'" *Wainwright v. Sykes*, 433 U.S. 72, 90, 97 S.Ct. 2497, 2508, 53 L.Ed.2d 594 (1977).

Bose Corp., 466 U.S. at 485; *see also Cybor*, 138 F.3d at 1466 (Mayer, C.J., and Newman, J., concurring) ("[T]hen the absence of review as a matter of right over *our* claim constructions, which may be new and unsupported by legal analysis, or may never have been tested by the adversarial process, would transform this court into a trial court of first and usually last resort.").

(c) Deferential Review of Factual Findings Underlying Claim Construction Will Promote Consistency

Deferential review is also required to avoid inconsistent appellate rulings on the same or similar fact findings underlying multiple patent law determinations. For example, when the determination of the level of skill in the art underlies the legal conclusions of obviousness and enablement, it is reviewed with deference. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (obviousness is a question of law with underlying factual inquiries including the level of ordinary skill in the art); *Enzo Biochem Inc. v. Calgene Inc.*, 188 F.3d 1362 (Fed. Cir. 1999) (factual determination of skill of those in the art underlying the legal conclusion of enablement is reviewed for clear error).[3]

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[3] Fact findings underlying legal conclusions for several other patent issues are reviewed with deference. *E.g., Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1573 (Fed. Cir. 1985) (anticipation is a question of fact, reviewed for clear error), *U.S. Envtl. Prods., Inc. v. Westall*, 911 F.2d 713, 715 (Fed. Cir. 1990) (facts underlying conclusion

(Continued on following page)

Thus, inconsistent rulings may result if a determination of the level of skill in the art is reviewed *de novo* for purposes of claim construction but reviewed for clear error for purposes of invalidity.

3. The Federal Circuit Failed to Give Deference to Factual Findings of the Trial Court Based on Lengthy Testimony on Complex Technology

The factual findings that underlie claim construction include the level of ordinary skill in the art at the time of filing; the background of the technology; and the customary meaning of technical claim terms to one of ordinary skill in the art. *See, e.g., Phillips*, 415 F.3d at 1340 (noting that extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art are available sources to show what one of skill in the art understood disputed claim term to mean).

During the trial court proceedings, the district court heard expert testimony on the background of the technology and the customary meaning of technical claim terms to assist in the court's interpretation of terms such as "therapeutically effective amount." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F.Supp.2d 202, 230 (D. Mass. 2004) ("*Amgen III*"). However, Judge Young felt caught in the conundrum of requiring extrinsic evidence to help understand the meaning of claim terms, while mindful of the Federal Circuit's narrow approach toward reliance on extrinsic evidence in claim construction. *Amgen III*, 339 F.Supp.2d at 226-28 n.23 ("How does a Court decipher the

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of whether there is a § 102(b) bar are reviewed under clearly erroneous standard); *Dippin' Dots Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007) (factual determinations underlying legal conclusion of inequitable conduct are reviewed for clear error).

plain and customary meaning of a term as understood by one skilled in the art without resorting to extrinsic evidence about how one skilled in the art would construe the term?"),[4] *see also id.* at 229 n.25; *id.* at 231 n.28; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1318 (Fed. Cir. 2006) ("*Amgen IV*") (Michel, C.J., dissenting-in-part) (noting extensive trial court proceedings, the court's creative step of employing a technical advisor on the underlying technology, extensive time spent rendering revised claim constructions and making extensive findings of fact and conclusions of law).

To eliminate this dilemma faced by trial courts, the SDIPLA urges the granting of *certiorari* and a holding that the District Court should find the facts necessary for claim construction, including the definition for one of ordinary skill in the art and the customary meaning of claim terms. Further, the holding in *Cybor*, that all aspects of claim construction are reviewed *de novo*, should be reversed.

B. THE FEDERAL CIRCUIT'S APPLICATION OF THE "FLEXIBLE RULE" GOVERNING REBUTTAL OF THE SURRENDER OF EQUIVALENTS RESURRECTS THE ABSOLUTE BAR REJECTED IN *FESTO*

In *Festo*, the Court re-affirmed that although the doctrine of equivalents renders the scope of patents less certain, such uncertainty is the necessary price for "ensuring the appropriate incentives for innovation." *Festo*, 535 U.S. at 723; *see also Warner-Jenkinson Co. v. Hilton*

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[4] *Cybor*, 138 F.3d at 1481 (Rader, J., dissenting) ("Surely the better view is to encourage judicial access to scientific evidence and findings based thereon. The ultimate beneficiary would be the parties, for the courts would be less restricted in the search for the correct and just result in patent cases.").

Davis Chem. Co., 520 U.S. 17, 29 (1997). Accordingly, although a narrowing amendment made for purposes of patentability may give rise to an estoppel that surrenders the territory between the original claim limitation and the amended claim limitation, *Festo*, 535 U.S. at 736, in some cases, "the amendment cannot reasonably be viewed as surrendering a particular equivalent," *id.* at 725.

The patentee may rebut the presumption that estoppel bars a claim of equivalence by showing "at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo*, 535 U.S. at 741. More specifically, there are three circumstances when an amendment cannot reasonably be viewed as surrender:

> The equivalent may have been unforeseeable at the time of the application; the rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question; or there may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question. In those cases the patentee can overcome the presumption that prosecution history estoppel bars a finding of equivalence.

Id. at 740-741.

Absent this opportunity to rebut the presumption of surrender of equivalents, a patentee who amended claims during prosecution could not exclude copiers making insubstantial changes to an invention. The value of patents would be substantially diminished, and innovation would be negatively impacted. Accordingly, "[t]he Court has consistently applied the doctrine in a flexible way, considering what equivalents were surrendered during a patent's prosecution, rather than imposing a complete bar

that resorts to the very literalism the equivalents rule is designed to overcome." *Festo*, 535 U.S. at 724.

This flexible approach toward the doctrine of equivalents recognized that a patentee should not be unduly punished for agreeing to narrow a claim during prosecution. *See Festo*, 535 U.S. at 738. An amended claim does not become "so perfect in its description that no one could device an equivalent . . . [t]he narrowing amendment may demonstrate what the claim is not; but it may still fail to capture precisely what the claim is." *Id.* "By amending the application, the inventor is deemed to concede that the patent does not extend as far as the original claim, *not that the amended claim is so perfect in its description that no one could devise an equivalent.*" *Id.* at 724 (emphasis added).

Following this Court's remand in *Festo*, Judge Newman cautioned that the Federal Circuit's "generous interpretation of the scope of surrender, and stinginess toward its rebuttal" in applying this Court's *Festo* standard for rebuttal created a framework that "few patentees can survive." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1385 (Fed. Cir. 2003) (Newman, J., concurring-in-part and dissenting-in-part). Judge Newman's forewarnings did not ring hollow. Indeed, in the five years since this Court decided *Festo*, only two patentees on appeal have successfully overcome the presumption of surrender of equivalents, invoking the "tangential relationship" test. *See Insituform Techs Inc. v. CAT Contracting Inc.*, 385 F.3d 1360, 1368 (Fed. Cir. 2004); *Primos Inc. v. Hunter's Specialties Inc.*, 451 F.3d 841, 849 (Fed. Cir. 2006). On appeal, no patentee has ever successfully rebutted the presumption based on foreseeability or "some other reason."

Even the one possible avenue for successfully rebutting the presumption of surrender has recently been further constrained by the Federal Circuit's cautioning

that "the tangential rebuttal principle remains very narrow." *Cross Med. Prods. v. Medtronic Sofamor Danek Inc.*, ___ F.3d ___, 82 USPQ2d 1065, 1075 (Fed. Cir. 2007) (Rader, J., concurring). The time is ripe for this Court to ensure that the Federal Circuit allows a patentee to "capture every nuance" of her invention by correctly applying its *Festo* standard to rebut the presumption of surrender of equivalents.

1. The Federal Circuit Applied the Wrong Test for Doctrine of Equivalents in *Amgen IV*

Although the Federal Circuit in *Amgen IV* purported to apply the Court's "tangential relation" test in determining whether Amgen successfully rebutted the *Festo* presumption of surrender of equivalents, it reformulated the test and made it impossible for the patentee to survive the analysis.

Judge Young correctly applied this Court's *Festo* test in determining that Amgen's amendment restricting the literal scope of the '080 patent to EPO having the complete amino acid sequence shown in Figure 6, was added only for purposes of limiting the '080 patent to human EPO products, and thus the amendment was no more than tangentially related to TKT's 165-amino acid equivalent. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 287 F.Supp.2d 126, 154 (D. Mass. 2003) ("*Amgen III (DOE)*"). The Federal Circuit, in overturning Judge Young's legally sound conclusion, however, applied its own novel standard: "the 165-amino acid equivalent is only tangential if the patentee's reason for limiting the '080 patent to EPO with 166 amino acids was unrelated to distinguishing the scope of the '080 patent from the scope of the '933 patent." *Amgen IV*, 457 F.3d at 1314. Thus, the Federal Circuit erroneously analyzed whether the amendment "for limiting the '080 patent to EPO with 166 amino acids" was made to "distinguish[]

the scope of the '080 patent from the scope of the '933 patent," *i.e.*, to overcome a double patenting rejection in light of the '933 patent. Essentially, the Federal Circuit stated that an equivalent is only tangential if the rationale for the amendment is unrelated to patentability.

However, as this Court enunciated, if the rationale for an amendment is unrelated to patentability, the presumption of prosecution history estoppel does not even apply. The Federal Circuit failed to properly consider whether "the rationale underlying the amendment" was tangentially related to the 165 amino acid equivalent, as required by a proper *Festo* analysis. *See Festo*, 535 U.S. at 736. For this reason, the Federal Circuit's ruling cannot stand.

2. The Determination of Whether the *Festo* Presumption Is Rebutted Is Based on Factual Underpinnings and Should Be Subject to Deferential Review

Like claim construction, a determination of whether a patentee has successfully rebutted the presumption of prosecution history estoppel is based on factual underpinnings that should be subject to deference on appellate review.

The Federal Circuit has held that the issue of whether a patentee has successfully rebutted a *Festo* presumption of surrender of equivalents is a question of law to be reviewed *de novo*. *Amgen IV*, 457 F.3d at 1312; *see, e.g., Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1357 (Fed. Cir. 2006); *Rhodia Chimie v. PPG Indus. Inc.*, 402 F.3d 1371, 1376 (Fed. Cir. 2005); *Ranbaxy Pharms., Inc. v. Apotex, Inc.*, 350 F.3d 1235, 1240 (Fed. Cir. 2003). However, in setting forth the general standard governing rebuttal of the presumption of surrender, the Federal Circuit recognized that factual findings may underlie this determination: "[b]y its very nature, objective unforeseeability depends on underlying factual issues relating to,

for example, the state of the art and the understanding of a hypothetical person of ordinary skill in the art at the time of the amendment. Therefore, in determining whether an alleged equivalent would have been unforeseeable, a district court may hear expert testimony and consider other extrinsic evidence relating to the relevant factual inquiries." *Festo*, 344 F.3d at 1369.

The Federal Circuit further stated that whether an amendment narrowed a claim for reasons tangential to the equivalent should be discernible "from the prosecution history record without the introduction of additional evidence, except, when necessary, testimony from those skilled in the art as to the interpretation of that record." *Festo*, 344 F.3d at 1370. Likewise, determination of rebuttal for "some other reason" should be limited to the prosecution history record. *Id.*

To the extent the Federal Circuit has asserted that the test for a "tangential relation" or "other reasons" rebutting the surrender of equivalents is based solely on the intrinsic evidence, this is not the case. This Court has noted that a determination of surrender of equivalents requires an analysis of extrinsic evidence. *See Festo*, 535 U.S. at 741 ("the patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent"). Judge Newman has also cautioned that the "tangential relation" and "some other reasons" tests are based on underlying fact:

> [T]he factors relevant to determination of tangential relation are unlikely to reside in the prosecution record, for unrelated subject matter or unknown equivalents are unlikely to have been discussed by either the examiner or the applicant. The issue of "tangentialness" may require consideration of how the reason for an amendment affected the patentee's view that certain technology was extraneous. The prosecution

> record rarely discusses devices that are not prior art.

Festo, 344 F.3d at 1384 (Newman, J., concurring in part and dissenting in part). Further, "[l]ike tangentialness, if some other reason arises that relates to the alleged equivalent, evidence would be more likely to reside outside of the prosecution record than within it." *Id.* at 1385.[5] Thus, like foreseeability, they should be established based on underlying questions of fact, and not law. *Id.* at 1383.

Appellate review should afford the trial court significant deference in factual findings underlying the determination of rebuttal of the surrender of equivalents. Continuing to indulge in the fiction that rebuttal is a question of law subject to *de novo* review not only leads to uncertainty and unpredictability about the finality of judgments at trial, but also prevents a district court from taking "full advantage of its unique ability to evaluate the relevant technology." Marc D. Sharp, *Festo X: The Complete Bar by Another Name?* 19 BERKELEY TECH. L.J. 111, 123-24 (2004).

IV. CONCLUSION

The SDIPLA therefore respectfully urges the Court to grant *certiorari* and hold that the District Court should find the facts necessary for claim construction. The holding in *Cybor*, that all aspects of claim construction are reviewed *de novo*, should be reversed. Moreover, the Court should reverse the Federal Circuit's ruling on the Doctrine of Equivalents, and direct the Federal Circuit to apply the

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[5] Judge Young also noted that an objective analysis as to whether "some other reason" reasonably prevented the patentee from describing the alleged equivalent may depend on underlying factual issues relating to the state of the art and the understanding of a hypothetical person of ordinary skill in the art at the time of the amendment. *Amgen III (DOE)*, 287 F.Supp.2d at 155.

correct test for whether the patentee rebutted the presumption of the surrender of equivalents. The SDIPLA further urges that the Court order that the Federal Circuit review with deference the fact findings underlying the district court's determination of rebuttal.

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